B10

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 August 2002 (08.08.2002)

PCT

(10) International Publication Number
WO 02/060872 A1

(51) International Patent Classification[7]: C07D 209/02, 307/80, 307/86, 333/16, 333/22, 333/26, 333/62, 495/04, C07C 45/72, 49/255, 49/755, 323/20, 323/22, C07J 71/00, A61K 31/404, 31/343, 31/381, 31/122, A61P 35/00

(21) International Application Number: PCT/AU02/00099

(22) International Filing Date: 1 February 2002 (01.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PR 2838 1 February 2001 (01.02.2001) AU

(71) Applicants *(for all designated States except US)*: **THE AUSTRALIAN NATIONAL UNIVERSITY** [AU/AU]; Acton, Australian Capital Territory 2601 (AU). **THE GOVERNMENT OF THE UNITED STATES as REPRESENTED by THE SECRETARY of THE DEPARTMENT of HEALTH and HUMAN SERVICES** [US/US]; National Institutes of Health, Office of Technology Transfer, 6011 Executive Blvd., Suite 325, Rockville, MD 20850 (US).

(72) Inventors; and

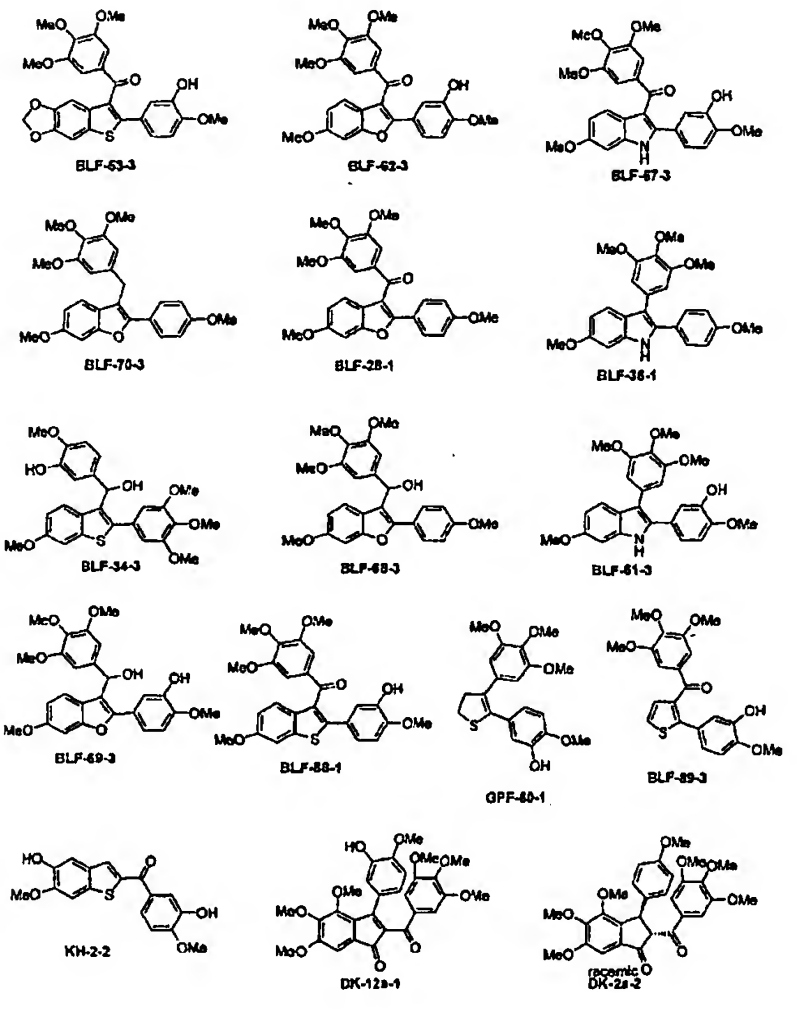
(75) Inventors/Applicants *(for US only)*: **FLYNN, Bernard, Luke** [AU/AU]; 22 Carroll Street, Hughes, Australian Capital Territory 2605 (AU). **HAMEL, Ernest** [US/US]; 5200 Benton Avenue, Bethesda, MD 20814-2861 (US).

(74) Agents: **DE BRUYN, Paula** et al.; Davies Collison Cave, 1 Little Collins Street, Melbourne, Victoria 3000 (AU).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

[Continued on next page]

(54) Title: SYNTHESIS FOR THE PREPARATION OF COMPOUNDS FOR SCREENING AS POTENTIAL TUBULIN BINDING AGENTS



(57) Abstract: The present invention relates to methods for the synthesis of chemical compounds for screening as potential tubulin polymerization inhibitors. The invention also provides chemical compounds with tubulin polymerization inhibitor activity.

WO 02/060872 A1

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Synthesis for the Preparation of Compounds for Screening as Potential Tubulin Binding Agents.

FIELD OF THE INVENTION

The present invention relates generally to chemical compounds and methods for their preparation. In particular, the invention relates to chemical compounds, and libraries thereof, which may possess useful therapeutic activity, and their use in methods of therapy as well as compositions containing said compounds.

BACKGROUND OF THE INVENTION

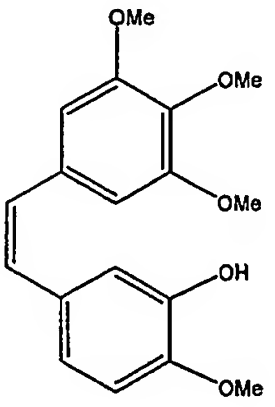
The search for effective chemotherapeutic drugs relies on the discovery and development of chemical compounds which possess biologically potent anti-tumour activities. While many naturally occurring compounds have been recognised as possessing this desirable activity, eg taxol, the inherent difficulties which may be associated with the isolation and purification of naturally occurring small quantities have prompted extensive efforts directed towards the chemical synthesis of analogues of these bioactive compounds and other potentially bioactive molecules.

Compound libraries prepared by combinatorial methods now play an increasing role in the discovery of bioactive molecules. These libraries can be subjected to high throughput screening methods which allow for the rapid identification of potential new drug candidates. More recently, such libraries have also found utility in molecular biology as an aid to understanding various biological pathways. To reduce the cost of drug discovery using these methods, efficient means of producing molecular diversity need to be identified. Traditionally, efficiency in synthesis has been defined as providing the maximum yield of a targeted product. In diversity-orientated synthesis, efficiently is redefined as providing the maximum range of different structural entities from the minimum number of starting components.

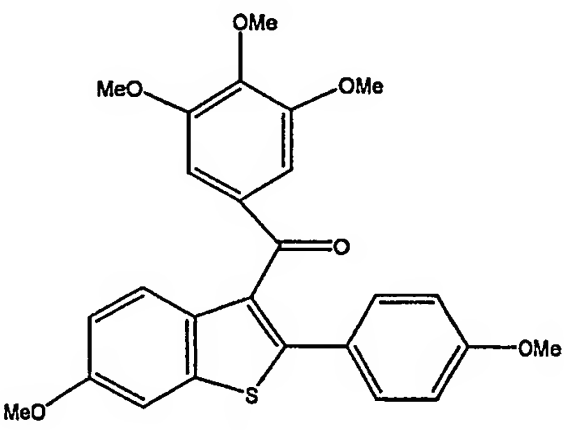
One class of compounds which have attracted attention are those which inhibit tubulin assembly and prevent its polymerization into microtubules. Compounds with

tubulin binding activity are thus effective anti-mitotic agents and include colchicine, vinblastine, vincristine and taxol. Another tubulin polymerization inhibitor which has attracted recent interest is Combretastatin A4 (A) which is a powerful inhibitor of tubulin polymerization with an IC_{50} value of ~2-3 μM and which has been shown to display potent and selective toxicity toward tumour vasculature. Its 3'-hydroxy disodium phosphate ester is currently the subject of clinical trial.

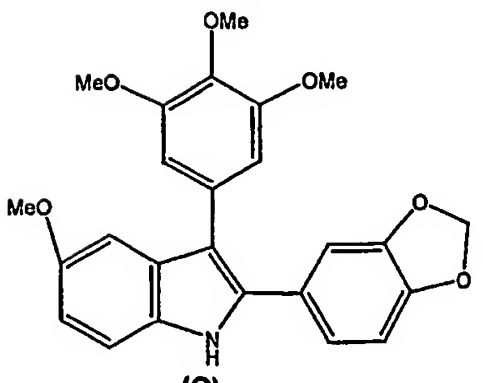
However, despite its promising activity, the compound readily isomerises to its inactive (E)-isomer and efforts have been directed towards the identification of configurationally stable analogues. Recently, independent researchers have identified compounds (B) (US Patent No. 5,886,025) and (C) (Madarde, M. *et al Bioorg, Med. Chem Lett.*, 1999, 2303) as showing moderate tubulin binding and anti-mitotic activity. However, in contrast, the benzofuran (D) did not exhibit tubulin binding activity (Banwell, M.G., *et al Aust J. Chem.*, 1999, **52**, 767-774).



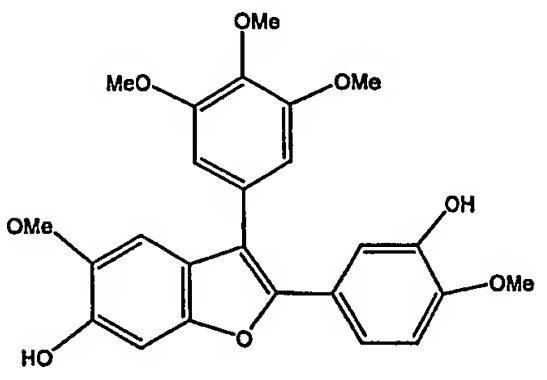
(A)



(B)



(C)



(D)

Accordingly, there exists a need for new synthetic methods which can allow for the generation of libraries of compounds which can be screened for desired bioactivities, such as tubulin binding and anti-mitotic activity, and for the discovery of new compounds which possess this activity.

It has now been found that a number of compounds prepared by new synthetic methods have been found to possess useful bioactivity. These compounds can be variously prepared from a small group of starting substrates to provide a combinatorial library of compounds which can be screened for bioactivity.

SUMMARY OF THE INVENTION

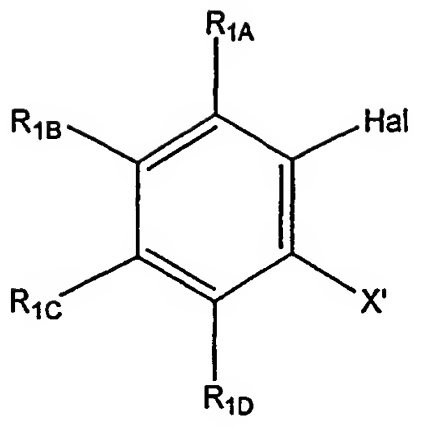
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

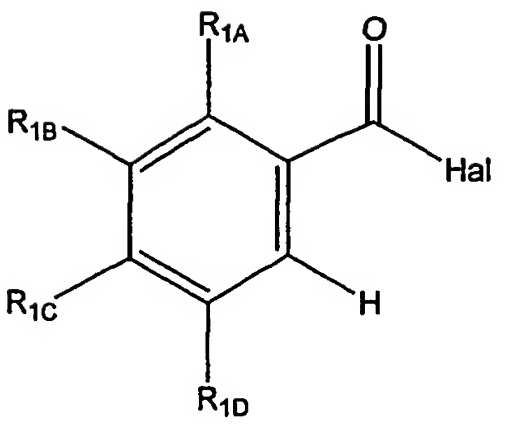
The present invention provides new methods for generating libraries of compounds including benzothiophenes, benzofurans, indoles, indanones and indenones, as well as non-benzo-fused analogues, for biological screening. The invention further provides new compounds which exhibit tubulin binding anti-mitotic activity, and processes for their preparation.

In a first aspect, there is provided a combinatorial library of 2 or more chemical compounds each compound comprising the reaction product derived from at least two substrates selected from (a), (b) and (c):

(a)

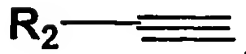
(i) 

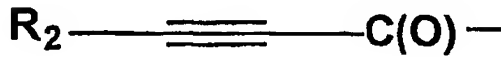
or

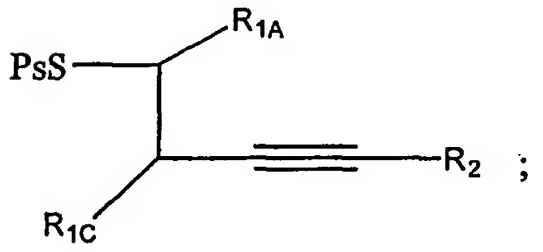
(ii) 

;

(b)

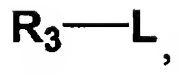
(i)  , or a metallated form thereof; or

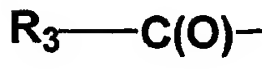
(ii)  ; or

(iii) 

;

(c)

(i)  , or a metallated form thereof wherein L is replaced by a metal; or

(ii)  ;

wherein

R_{1A}-R_{1D} are independently selected from hydrogen, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino or any 2 adjacent R_{1A}-R_{1D} together form

–O-CH_2-O-;

Hal is I, Br or Cl;

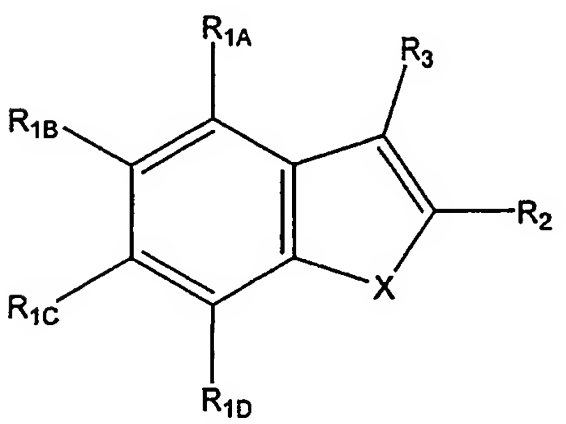
X' is OH, SPs (wherein Ps is a sulfur-protecting group capable of stabilising a positive charge), NP_N (wherein P_N is a nitrogen-protecting group), or NHR (wherein R is sulfonyl, trifluoroacyl, C_{1-7}acyl, C_{1-6}alkyl, or an aryl group);

R_2 and R_3 are optionally substituted aryl groups;

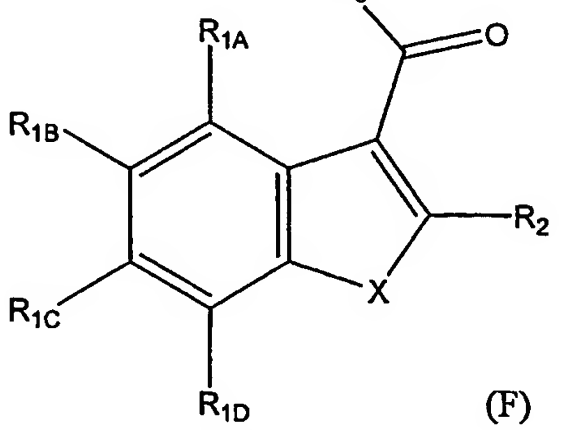
L is a leaving group.

In another aspect, the invention provides for combinational library of compounds for screening, as potential tubulin polymerisation inhibitors, said library comprising two or more compounds of formulae (E) to (Q), said compounds being the reaction products of the following substrates:

- (a)(i), (b)(i) and (c)(i) to produce compounds of formulae (E) and (F)



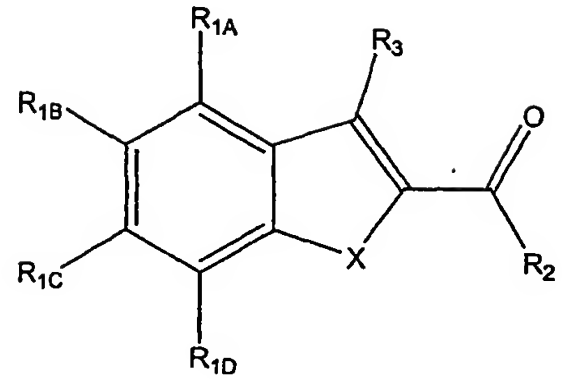
(E)



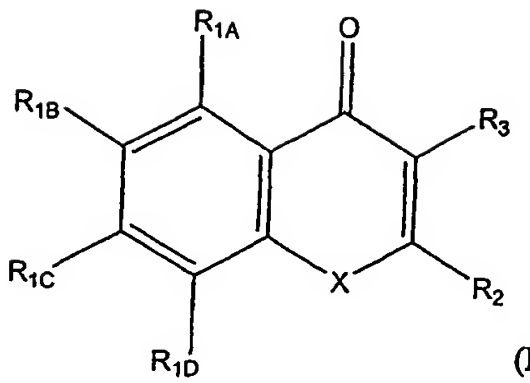
(F)

- (a)(i), (b)(i) and (c)(ii) to produce compounds of formula (F);

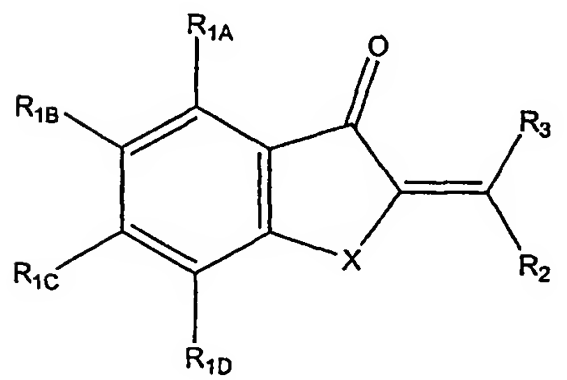
- (a)(i), (b)(ii) and (c)(i) to produce compounds of formulae (G), (H), (I), (J) or (K)



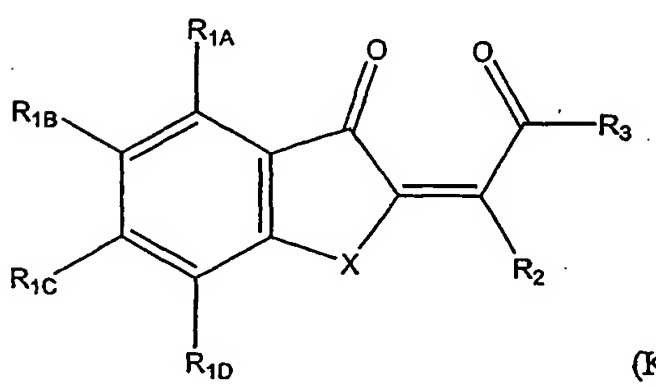
(G)



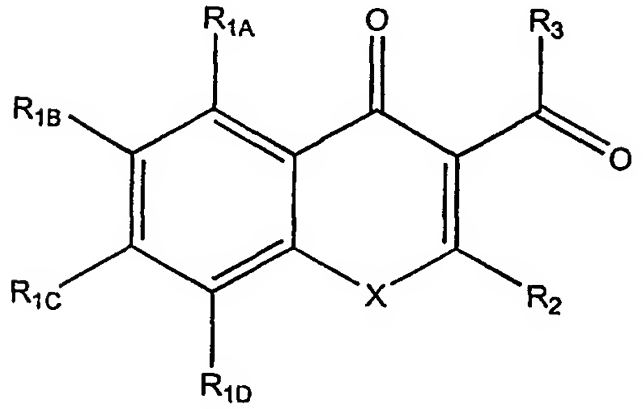
(H)



(J)

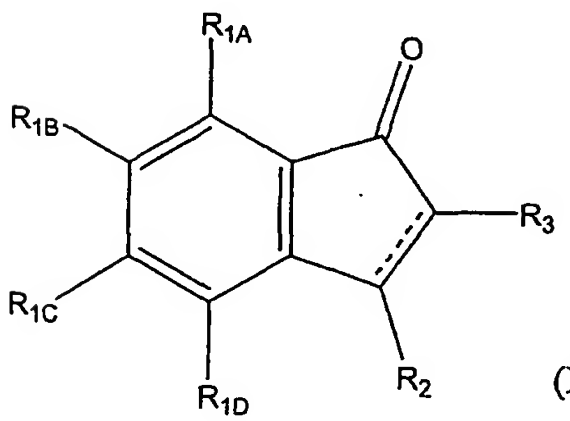


(K)



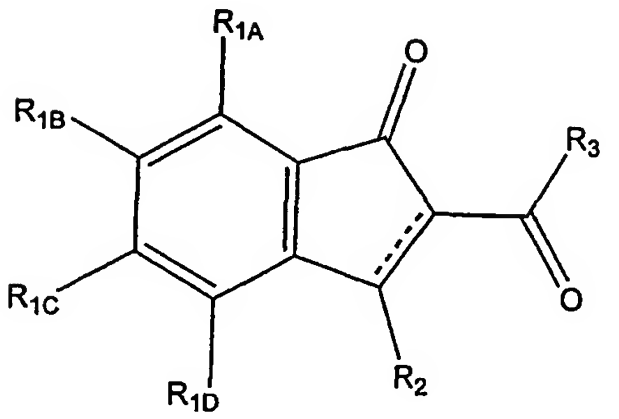
(I)

- (a)(i), (b)(ii) and (c)(ii) to produce compounds of formulae (I) and (K)
- (a)(ii), (b)(i) and (c)(i) to produce compounds of formula (L)



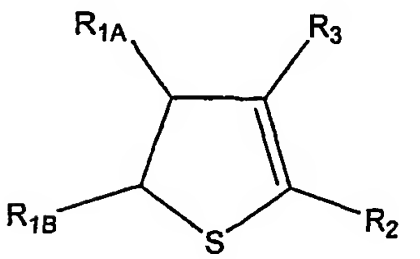
(L)

- (a)(ii), (b)(i) and (c)(ii) to produce compounds of formula (M)



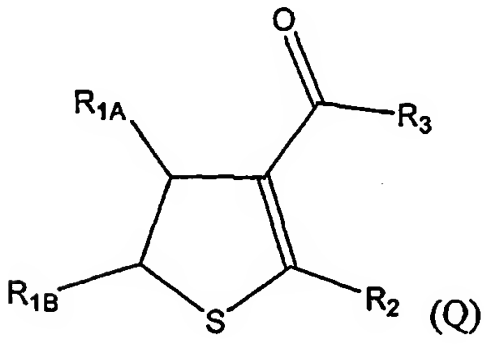
(M)

- (b)(iii) and (c)(i) to produce compounds of formula (P)



(P)

- (b)(iii) and (c)(ii) to produce compounds of formula (Q)

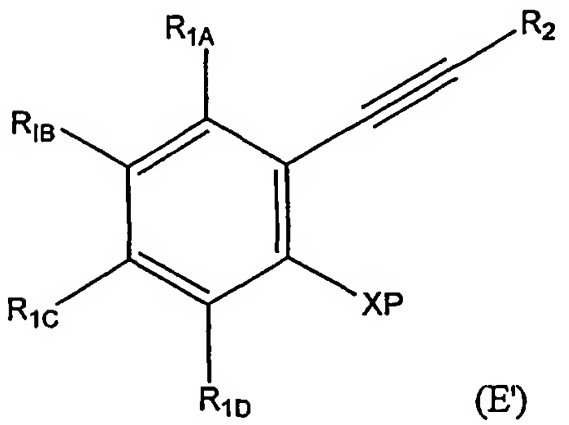


(Q)

wherein R_2, R_3, $R_{1A} - R_{1D}$, (a)(i), (a)(ii), (b)(i)-(b)(iv) and (c)(i)-(iii) are as defined above, and X=O, S, or NR (wherein R is H, sulfonyl, C_{1-6}alkyl, C_{1-7}acyl, or an aryl group).

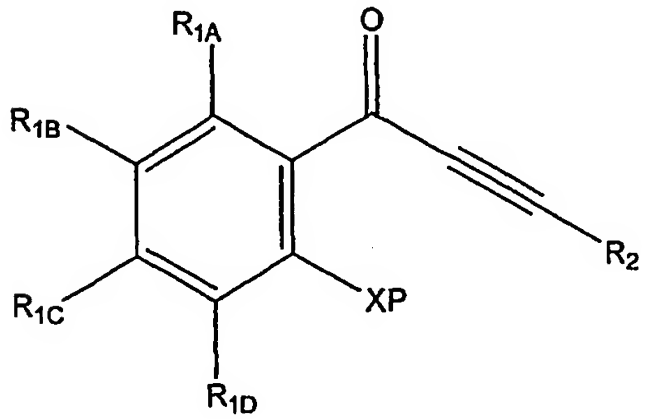
In a further aspect the present invention provides a combinational library of intermediates useful for the preparation of compounds of formulae (E) – (Q), said intermediates being the reaction products of the following substrates;

- (a)(i) and (b)(i) to produce intermediates of formula (E') for use in preparing compounds of formulae (E) and (F)

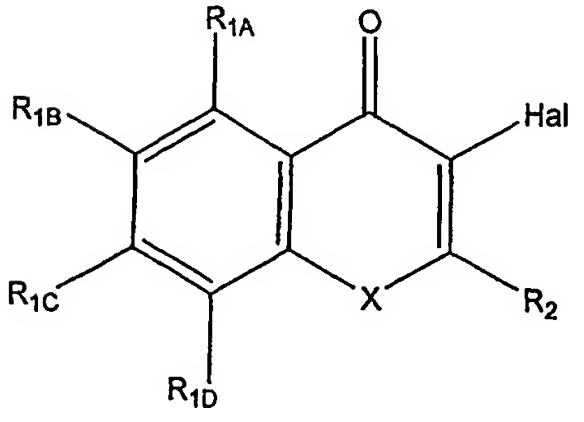


(E')

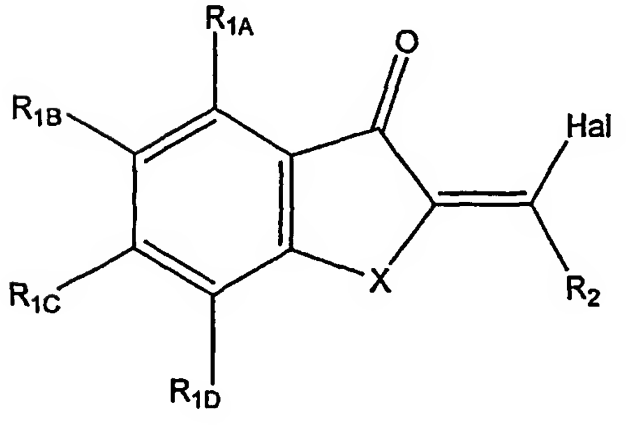
- (a)(i) and (b)(ii) to produce intermediates of formulae (F'), (G') and (H') for use in preparing compounds of formulae (G), (H), (I), (J) or (K);



(F')

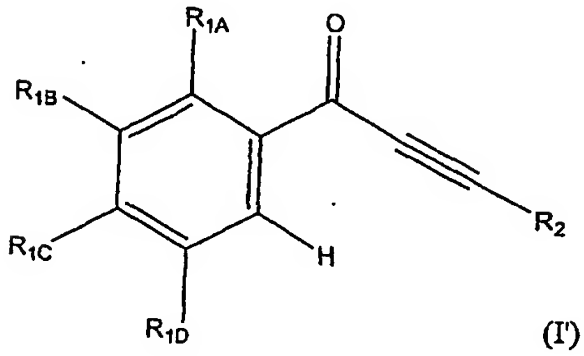


(G')

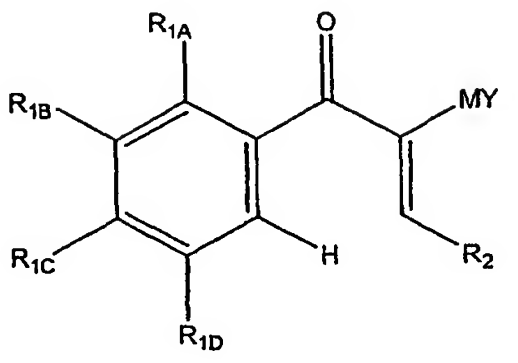


(H')

- (a)(ii) and (b)(i) to produce intermediates of formulae (I') and (J') for use in preparing compounds of formula (L) or (M)

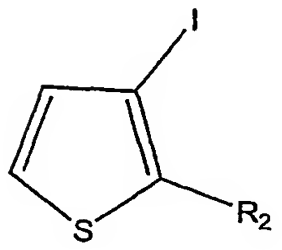


(I')



(J')

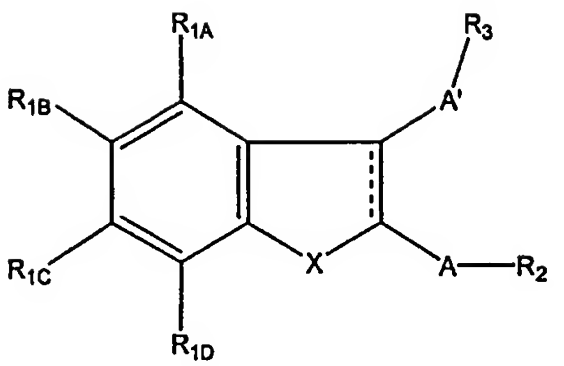
- (b)(iii) with itself to produce intermediates of formulae (L')



(L')

for use in preparing compounds of formulae (P) and (Q);
wherein R_{1A}-R_{1D}, R_2, R_3, X (a)(i), (a)(ii), (b)(i)-(iv) and (c)(ii)-(iii)are as defined above, X is N, O or S, P is a protection group and MY is $Sn(alkyl)_3$ or $B(OR)_2$, wherein R is H or alkyl.

In another aspect, the invention provides a combinatorial library of at least two compounds of formula (I):



(I)

wherein

X is selected from O, S, NR, C=O (R is H, C_{1-6}alkyl or C_{1-6}acyl);

A and A' are independently selected from CH_2, C=O, CH(OR') (R' is H, C_{1-6}alkyl, C_{1-7}acyl) or a single bond; provided that when one of A or A' is CH_2, C=O or CH(OR), then the other is a single bond and that when X is S or NH, A is CH_2, C=O or CH(OR);

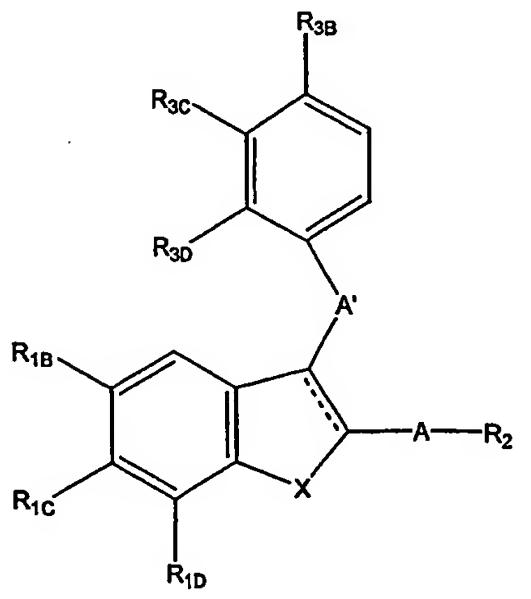
..... is a double bond when X is O, S or NR; or

is a single or double bond when X is C=O.

R_{1A}- R_{1D} are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino, optionally substituted acylamino or any 2 adjacent R_{1A}-R_{1D} together form –O-CH_2-O-.

R_2 and R_3 are optionally substituted aryl groups.

In a further aspect the invention provides a compound of formula (I''''')



(I''''')

wherein X is O, S, NR (wherein R is hydrogen, sulfonyl, C_{1-6}alkyl, C_{1-7}acyl, or an aryl

group) or C=O; and

R_{1B}-R_{1D} and R_{3B}-R_{3D} are independently selected from hydrogen, hydroxy, methoxy, and amino or any 2 adjacent R_1 and/or R_3 groups from R_{1B}-R_{1D} and R_{3B}-R_{3D} form a dioxolanyl group;

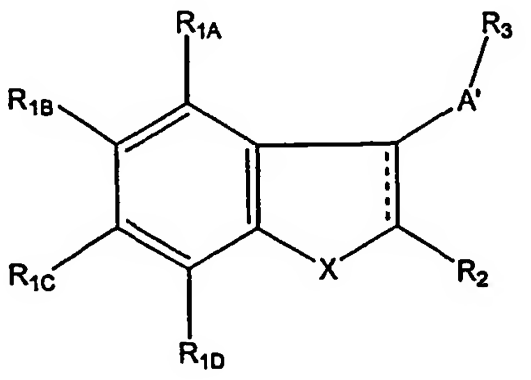
R_2 is an optionally substituted aryl group;

A and A' are independently selected from the group consisting of a single bond, C=O, CH_2, and CH(OR'), (wherein R' is hydrogen, C_{1-6}alkyl or C_{1-7}acyl); and

provided that the compound is not;
3-(3',4',5'-trimethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(2',6'-dimethoxybenzoyl-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(3',5'-dimethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(3',4'-dimethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(4'-methoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(4'-ethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(3',4',5'-triethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-[3'-(3',4',5'-trimethoxyphenyl)propionyl]-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(3',4',5'-triethoxybenzoyl)-2-(4'-ethoxyphenyl)-6-ethoxybenzo[b]thiophene;
3-(4'-ethoxy-3',5'-dimethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(4'-N,N-dimethylaminobenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(3',4',5'-triflurobenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(2',3',4',5',6'-pentafluorobenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(3',4',5'-trimethoxybenzoyl)-2-(4'-methoxyphenyl)-benzo[b]thiophene;
3-(3',4',5'-trimethoxybenzoyl)-2-(4'-ethoxyphenyl)-6-ethoxybenzo[b]thiophene;
3-(4'-hydroxy-3',5'-dimethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
2-(3',4',5'-trimethoxybenzoyl)-3-(4'-methoxyphenyl)-6-methoxybenzo[b]furan;

2-(4'-methoxyphenyl)-3-(3',4',5'-trimethoxybenzoyl)-6-methoxyindole;
2-(3'-*t*-butylsiloxy-4'-methoxyphenyl)-3-(3',4',5'-trimethoxybenzoyl)-6-methoxyindole;
Disodium 2-(4'-methoxyphenyl-3'-O-phosphate)-3-(3",4",5"-trimethoxybenzoyl)-6-methoxyindole;
2-(4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;
Disodium 2-(3'-phosphormaidate-4'-methoxyphenyl)-3-(3", 4",5"-trmethoxybenzoyl)-6-methoxyindole;
2-(3'-hydroxy-4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;
2-(3'-amino-4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;
Disodium 2-[(4'-methoxyphenyl)-3'-O-phosphate]-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;
2-(3'-diethylphosphoramidate-4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;
Disodium 2-(3'-phosphoramidate-4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;
2-(1-napth-1-yl)-3-(3",4",5"-trimethoxyphenyl)-5-methoxyindole;
2-(3,4-methylenedioxyphenyl)-3-(3",4",5"-trimethoxyphenyl)-5-methoxyindole;
2-(furan-2-yl)-3-(3', 4', 5'-trimethoxyphenyl)-5-methoxyindole;
2-(furan-3-yl)-3-(3', 4', 5'-trimethoxyphenyl)-5-methoxyindole;
2-(5-methylfuran-2-yl)-3-(3', 4', 5'-trimethoxyphenyl)-5-methoxyindole.

In a further aspect, the invention provides a method of preparing a compound of formula (I')



(I')

wherein

X is O, NH or NR, (wherein R is H, sulfonyl C_{1-6}alkyl or C_{1-7}acyl);

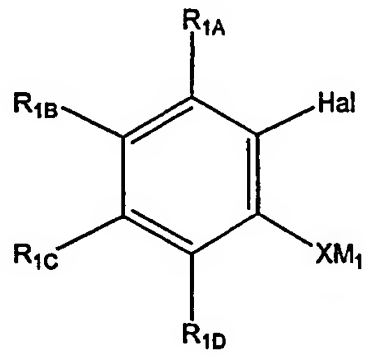
A' is independently selected from a single bond, CH_2, C=O, and CH(OR') (wherein R' is H, C_{1-6}alkyl or C_{1-7}acyl);

R_{1A}-R_{1D} are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino, optionally substituted acylamino, or any 2 adjacent R_{1A}-R_{1D} together form –O-CH_2-O-;

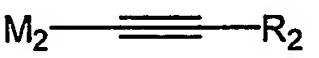
R_2 and R_3 are optionally substituted aryl groups;

said method comprising the steps of:

a) coupling a compound of formula (1) with an alkyne of formula (2) in the presence of a nickel or palladium coupling agent



(1)



(2)

wherein

R_{1A}-R_{1D}, R_2 and X are as above;

Hal is I ,Br or Cl;

M_1 is a metal or a metal species therof, said metal selected from the group consisting of Li, Na, K, Mg, Cs and Ba;

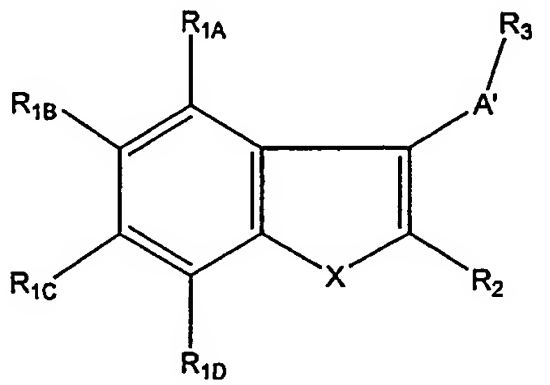
M_2 is a metal, or a metal species thereof, said metal selected from the group consisting of Mg, Zn, Cu, B, Si, Mn, Sn, Ge and Al;

X is O or NR (wherein R is sulfonyl, C_{1-6}alkyl, or C_{1-7}acyl);

b) reacting *in situ* the resulting coupled product with R_3-L, wherein R_3 is an optionally substituted aryl group and wherein L is a leaving group, optionally in the presence of carbon monoxide; and

c) optionally reducing the resulting product, when A' is C=O, to afford compounds in which A' = CH_2 or CH(OR').

In yet another aspect, the invention provides a method for preparing a compound of formula (I''):



(I'')

wherein

X is S;

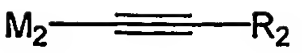
A' is selected from a single bond, CH_2, C=O, and CH(OR') (wherein R' is H, C_{1-6}alkyl or C_{1-7}acyl);

R_{1A}-R_{1D} are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino, optionally substituted acylamino, or any two adjacent R_{1A}-R_{1D} together form -O-CH_2-O-;

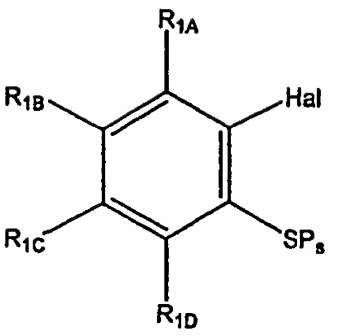
R_2 and R_3 are optionally substituted aryl groups;

said method comprising the steps of:

a) coupling a compound of formula (3) with a compound of formula (4) in the presence of a nickel or palladium coupling agent



(3)

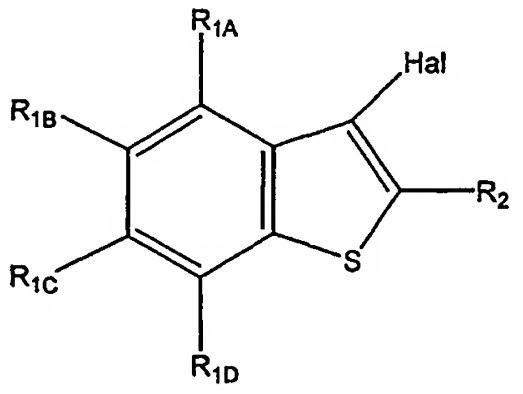


(4)

wherein

R_{1A}-R_{1D}, Hal, M_2 and R_2 are as above, and P_s is a sulfur protecting group capable of stabilizing a positive charge;

b) cyclising the resulting coupled product in the presence of a Hal^+ producing reagent to give (5)



(5)

wherein

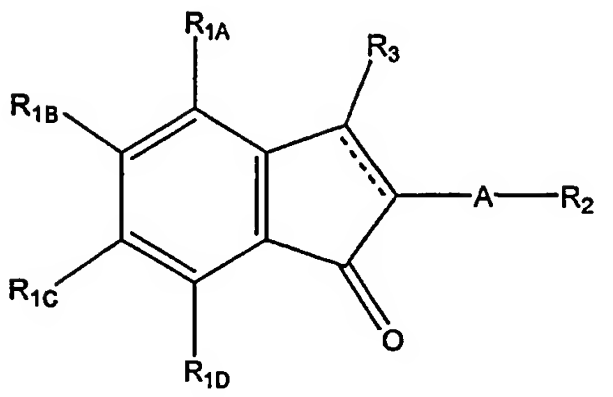
Hal is Cl, Br or I;

c) coupling (5) with either the moiety R_3-C(O)- or R_3-

wherein R_3 is an optionally substituted aryl group; and

d) optionally reducing the coupled product when A' is C=O, to afford compounds in which A' = CH_2 or CH(OR').

In another aspect, the invention provides a method for preparing a compound of formula (I''')



(I''')

wherein

A is selected from a single bond, CH_2, C=O and CH(OR') (wherein R' is H, C_{1-6}alkyl or C_{1-7}acyl);

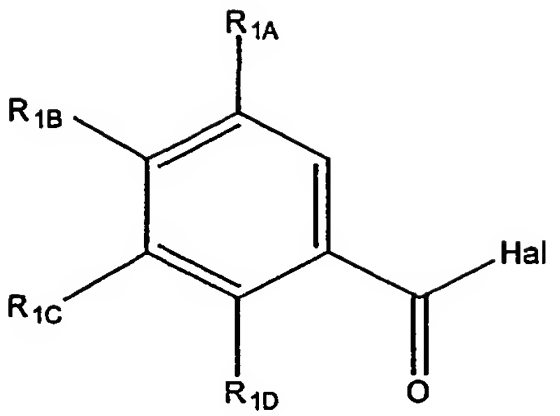
R_{1A}-R_{1D} are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino or any 2 adjacent R_{1A}-R_{1D} together form $-O-CH_2-O$;

..... is an optional double bond;

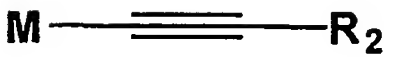
R_2 and R_3 are optionally substituted aryl groups;

said method comprising the steps of:

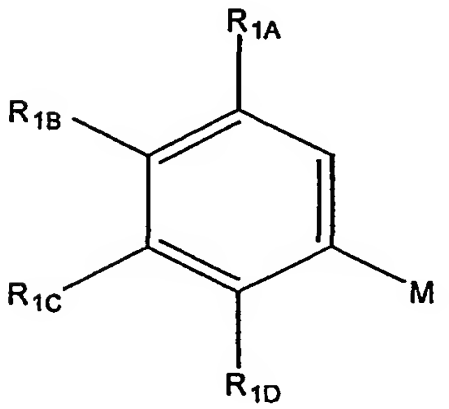
(a) reacting compound (6) with compound (7) or reacting compound 6(a) with compound 7(a).



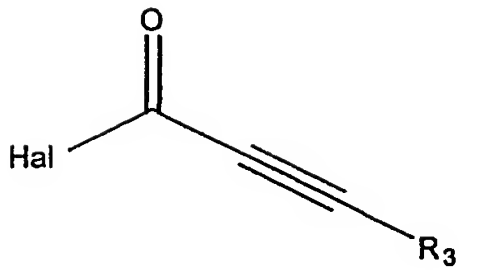
(6)



(7)

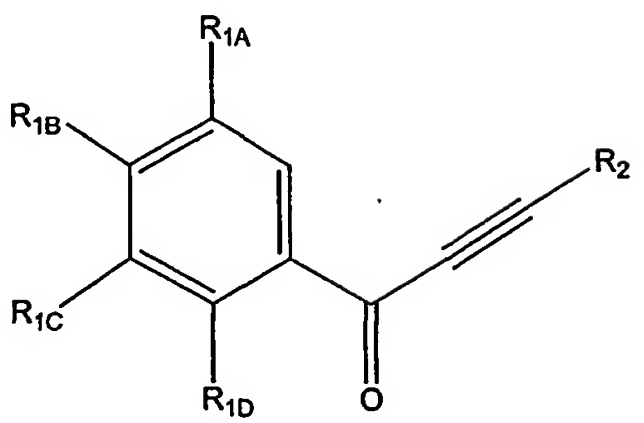


(6a)



(7a)

to form a compound (9)

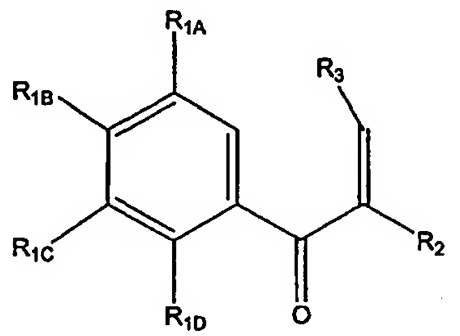


(9)

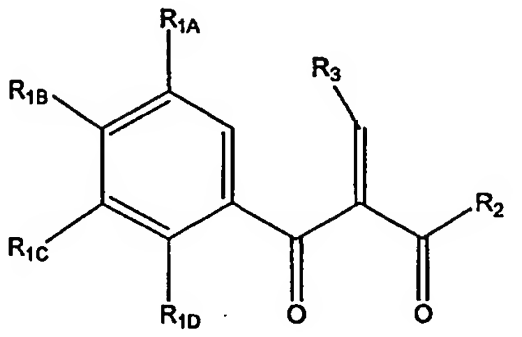
wherein
M is Li, Na, K or MgHal (Hal is Br, Cl or I);

b) treating compound (9) with a metal hydride in the presence of a palladium coupling agent;

c) coupling the resulting product with R_3-Hal or R_3-C(O)-Hal (wherein Hal is Cl, Br or I) to provide either compound (10) or (11); and



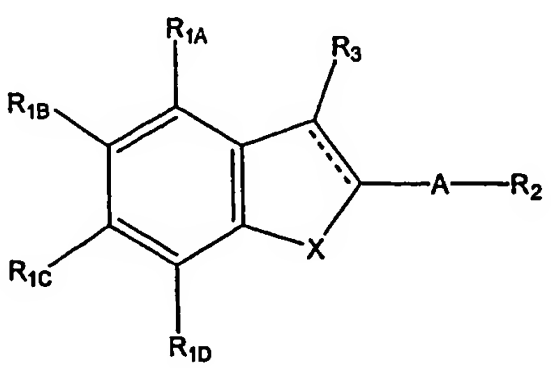
(10)



(11)

(d) cyclising (10) or (11) under acidic conditions to form an indanone and optionally treating the cyclised product with an oxidising agent to form an indenenone.

In yet a further aspect, the invention provides a method for preparing a compound of Formula (I'''')



(I'''')

wherein;

X is O, S or NR (wherein R=H, C_{1-6}alkyl or $C(O)C_{1-6}$alkyl);

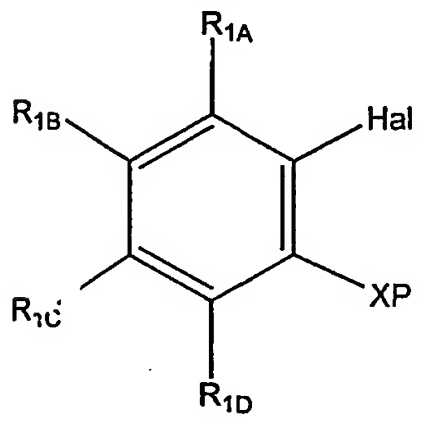
R_{1A}-R_{1D} are as previously defined;

A is C=O, CH_2 or CH(OR') (wherein R' is H, C_{1-6}alkyl or C_{1-7}acyl);

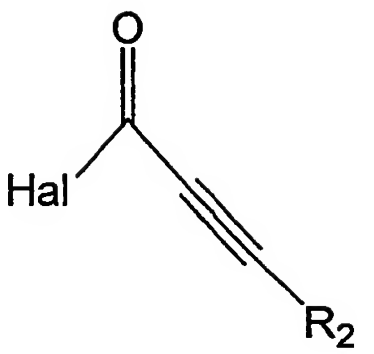
R_2 and R_3 are optionally substituted aryl groups;

comprising the steps of

a) coupling a compound (12) with compound (13)



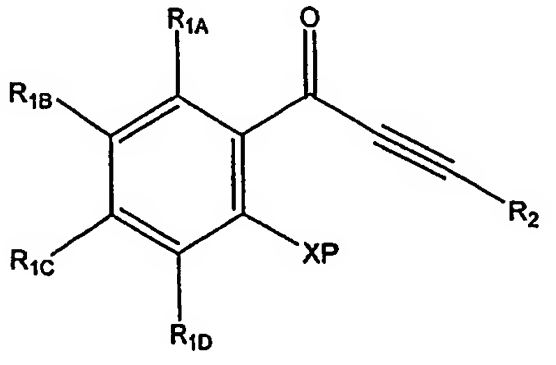
(12)



(13)

wherein Hal is Cl, Br, or I ;

to form a compound of formula (14);



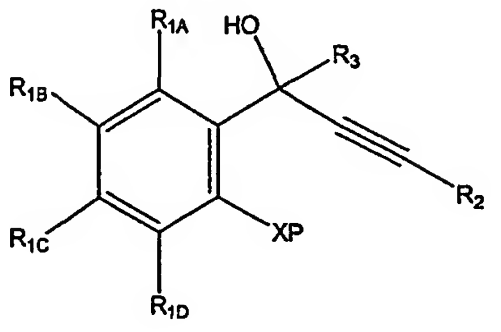
(14)

b) when X is S, protecting the thiol with a sulfur-protecting group

c) reacting (14) with a compound

wherein

M_1 is Li, Na, K, Mg, Cs or Ba, and R_3 is an optionally substituted aryl group; to form



(15)

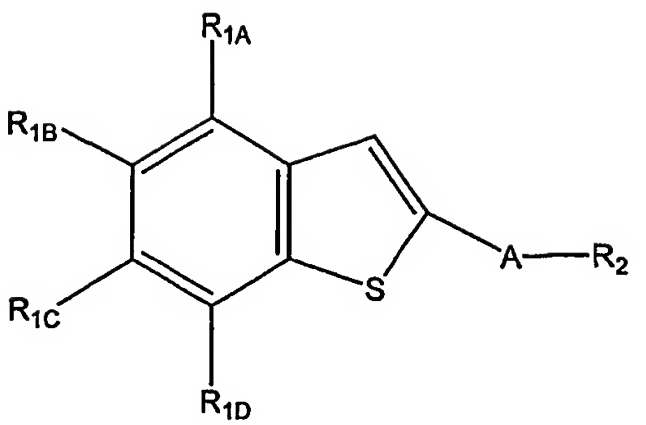
wherein

when X is O or NH, then P is H and when X is S, P is a sulfur protecting group and when XP is NR, R is a hydrogen, sulfonyl, C_{1-6}alkyl, C_{1-7}aryl or an aryl group;

d) treating (15) with a Hal^+ producing reagent, to afford cyclisation;

e) and optionally reducing the cyclised product when A'=CO, to afford libraries of compounds in which A'=CH_2 or CH(OR').

Still another aspect of the invention provides a compound of Formula II



(II)

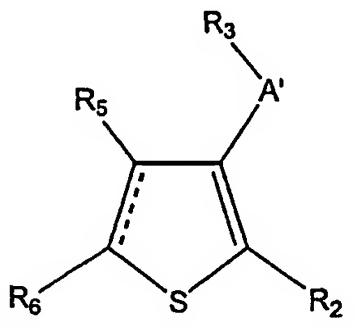
wherein

R_{1A}-R_{1D} are independently hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino or 2 adjacent R_{1A}-R_{1D} are O-CH_2-O;

R_2 and R_3 are optionally substituted aryl groups;

A is C=O, CH_2 or CH(OR') (R'=H, C_{1-6}alkyl or C_{1-7}acyl).

Still yet a further aspect of the invention relates to compounds of Formula (III)



(III)

wherein

R_2 and R3 are optionally substituted aryl groups;

A' is CO, CH_2, CH(OR') (wherein R'=H, C_{1-6}alkyl or C_{1-7}acyl) or a single bond;

R_5 and R_6 can independently be hydrogen, optionally substituted alkyl, optionally substituted aryl or optionally substituted alkenyl;

..... is an optional double bond.

Other aspects of the invention relate to combinatorial libraries of compounds comprising at least two compounds of Formula (I'), (I''), (I''') (I''''), (II) or (III).

Still other aspects of the invention relate to the use of the compounds of the present invention in the manufacture of medicaments, and methods thereof, in the treatment of conditions requiring tublin polymerization inhibitors.

BRIEF DESCRIPTION OF THE DRAWINGS

The drawings which follow form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

Figure 1 - schematically depicts a generalised "one pot" synthesis of benzofused furans and indoles.

Figure 2 - schematically depicts a generalised "one pot" synthesis of benzofused furans and indoles.

Figure 3 - schematically depicts a generalised synthesis of benzofused thiophenes.

Figure 4 - schematically depicts a generalised synthesis of benzofused thiophenes, including compound (B) from US Patent No. 5,886,025.

Figure 5 - schematically depicts a generalised synthesis of benzofused thiophenes.

Figure 6 - schematically depicts a generalised synthesis of benzofused thiophenes.

Figure 7 - schematically depicts a generalised "one pot" synthesis of aryl substituted α, β-alkenyl carbonyl compounds, for the preparation of indanones and indenones.

Figure 8 - schematically depicts a generalised synthesis of benzofused furans, indoles and thiophenes.

Figure 9 - schematically depicts a generalised synthesis of benzofused thiophenes.

Figure 10 - schematically depicts a generalised synthesis of thiophenes.

Figure 11 - depicts the structures of some of the preferred compounds of the present invention which posses TPI activity.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "alkyl", used either alone or in compound words such as "alkylamino" and "dialkylamino" etc, denotes straight chain, branched or cyclic alkyl, preferably C_{1-20} alkyl, eg C_{1-10} or C_{1-6}alkyl. Examples of straight chain and branched alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethyl-propyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, l,l-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2,-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methylhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethyl-pentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, 6-methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyl-octyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-, 2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl, undecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-ethylnonyl, 1-, 2-, 3-, 4- or 5-propylocytl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propylnonyl, 1-, 2-, 3- or 4-butyloctyl, 1-2-pentylheptyl and the like. Examples of cyclic alkyl include mono- or polycyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like. Where an alkyl group is referred to generally as "propyl", butyl" etc, it will be understood that this can refer to any of straight, branched and cyclic isomers where appropriate. "Alkoxy" refers to an alkyl when conveniently bonded to an oxygen atom. An alkyl

group may be optionally substituted by one or more optional substituents as herein defined. Accordingly, "alkyl" as used herein is taken to refer to optionally substituted alkyl. Optional substituents for an alkyl group include hydroxy, halo, alkoxy, phenyl, benzyl, phenoxy, benzyloxy, carbonyl, amino, acyl, acyloxy, alkylamino, dialkylamino, acylamino. Particularly preferred optional substituents include those wherein the alkyl moiety of the substituent is C_{1-6}alkyl. An alkyl group may also contain one or more degrees of unsaturation and therefore, alkyl may also include groups as described above containing one or more double or triple bonds.

Optionally substituted alkoxy, alkylamino, dialkylamino,refers to the optional substitution of the "alkyl" moiety. Similarly, optionally substituted, acyl, acylamino and acyloxy refer to the optional substitution of the alkyl or aryl moieties of the acyl group.

The term "alkenyl" as used herein denotes groups formed from straight chain, branched or cyclic hydrocarbon residues containing at least one carbon to carbon double bond including ethylenically mono-, di- or poly-unsaturated alkyl or cycloalkyl groups as previously defined, preferably C_{1-20} alkenyl (eg C_{1-10} or C_{1-6}). Examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1-4,pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl. An alkenyl group may be optionally substituted by one or more optional substitutents as herein defined. Accordingly, "alkenyl" as used herein is taken to refer to optionally substituted alkenyl.

Unless indicated otherwise, the term "halogen", "halo" "halide" etc. denotes fluorine, chlorine, bromine or iodine (fluoro, chloro, bromo or iodo) (fluoride, chloride, bromide iodide).

The term "aryl" includes single, polynuclear, conjugated and fused residues of aromatic hydrocarbon ring systems. Examples of hydrocarbon based "aryl" include phenyl, biphenyl, terphenyl, quaterphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, idenyl, azulenyl, chrysenyl. The term "aryl" also includes cyclic (single, polynuclear, fused or conjugated) hydrocarbon residues where one or more carbon atoms are replaced by a heteroatom and form an aromatic residue where two or more carbon atoms are replaced, this may be by the same heteroatom or different heteroatoms. Suitable heteroatoms include O, N, S and Se. Such aryl residues can be referred to as "heteroaryl". Suitable heteroaryl include furanyl, thieuyl, pyrrolyl, indolyl, pyridyl, pyridazinyl, pyrazoly, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl and benzothienyl. An aryl group may be substituted by one or more substituents and accordingly "aryl" is taken herein to refer to optionally substituted aryl. Preferred optional substituents include are independently selected from hydrogen, hydroxy, alkoxy, alkyl, acyloxy, amino, alkylamino, dialkylamino or any 2 adjacent positions are substituted to together form $-O-CH_2-O$. An aryl group may also be optionally fused to a cyclic or polycyclic group (saturated or unsaturated), which itself may be further optionally substituted as described for "alkyl" above.

The term "acyl" either alone or in compound words such as "acyloxy", or "acylamino" etc, denotes a group containing the moiety C=O (and not being a carboxylic acid, ester or amide or thioester) Preferred acyl includes C(O)-R, wherein R is hydrogen or an alkyl, or aryl preferably a C_{1-20} residue. C_{1-7}acyl refers to an acyl group that counts the carbonyl group as one carbon atom. Examples of acyl include formyl; straight chain or branched alkanoyl such as, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl; cycloalkylcarbonyl such as cyclopropylcarbonyl cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl; aroyl such as benzoyl, toluoyl and naphthoyl; aralkanoyl such as phenylalkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutylyl, phenylpentanoyl and

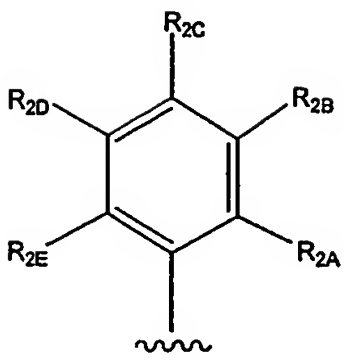
phenylhexanoyl) and naphthylalkanoyl (e.g. naphthylacetyl, naphthylpropanoyl and naphthylbutanoyl]. The term "acyloxy" refers to an acyl group covalently bonded to an oxygen atom.

As used herein, the term "protecting group", refers to an introduced functionality which temporarily renders a particular functional group inactive under certain desired conditions. Suitable protecting groups are known to those skilled in the art, for example as described in *Protective Groups in Organic Synthesis* (T.W. Greene and P.G.M. Wutz, Wiley Interscience, New York, 3rd edition).

As used herein, the term "leaving group" refers to a chemical group which is displaced by a nucleophile. Suitable leaving groups include those with the ability to stabilise the negative charge which it carries such as the halogens (e.g. I, Br, Cl), triflate (e.g. trifluoromethane sulfonyl), acetate and sulfonates (eg. tosylate, mesylate, nosylate etc). Some preferred leaving groups are I, Br, Cl and trifluoromethane sulfonyl.

In preferred embodiments of the invention, R_{1A}-R_{1D} include hydrogen, hydroxy, optionally substituted C_{1-6}alkoxy, optionally substituted C_{1-6}alkyl, optionally substituted C(O)-C_{1-6}alkyl, amino, optionally substituted optionally substituted C_{1-6}alkylamino, optionally substituted diC_{1-6}alkylamino or 2 adjacent R_{1A}-R_{1D} form a dioxolanyl group (-O-CH_2-O). Particularly preferred R_{1A}-R_{1D} include: hydrogen, hydroxy, methoxy, ethoxy, propoxy, butoxy, methyl, ethyl, propyl, butyl, acetyl, acetyloxy, amino, methylamino, ethylamino, propylamino butylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino or 2 adjacent R_{1A}-R_{1D} form a dioxolanyl group.

In yet other preferred embodiments of the invention, R_2 and R_3 can be independently an optionally substituted phenyl group of formula (i):



(i)

wherein

R_{2A}-R_{2E} are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino, optionally substituted acylamino or where any two adjacent R_{2A}-R_{2D} together form –O-CH_2-O-. Preferred R_{2A}-R_{2E} are as for R_{1A}-R_{1D} described above. Preferred forms of formula (i) are where R_{2A}-R_{2E} are independently hydrogen, hydroxy, methoxy, amino or any two adjacent R_{2A}-R_{2D} together form –O-CH_2-O-.

Where A or A' is CH_2 or CH(OR') these can be formed by the reduction of, C=O using a suitable reducing agent such as $LiAlH_4$ or $NaBH_4$. Alternatively, a CH(OH) group can be oxidized up to the carbonyl .

In the process for the preparation of compounds of Formula (I'), compounds (1) and (2) are derived from their respective phenol or protected amine and terminal alkyne respectively. The starting phenol or aniline and terminal alkyne can be coupled together under conditions which allow for the heteroannulation to spontaneously occur so as to form the target benzo[b]furan or indole in a "one-pot" synthetic strategy. Thus, the metal based compound required to form (1) must be such that the phenol or protected amine is deprotonated to form the group –OM_1 or NHM_1.

Suitable M_1 are based on Li, Na, K, Mg, Cs and Ba as well as species formed thereform, for example from Grignard reagents C_{1-4}alkyl MgHal (Hal = I, Cl or Br) . Suitable metal species include MgCl, MgBr or MgI. Formation of (1) can be effected by treating the corresponding phenol or protected amine with, for example, Li_2CO_3, Na_2CO_3,

K_2CO_3, $MgCO_3$, Cs_2CO_3, $BaCO_3$, MeMgCl, EtMgCl, MeMgBr, EtMgBr, MeMgI and EtMgI.

M_2 can be a hydrogen atom or metal species used in any palladium or nickel cross-coupling protocols known in the art, (for example, Stille, Suzuki or Negishi cross-coupling reactions using stannanes (eg aryl or alkylstannanes, boronic acids/esters or zinc based compounds eg. ZnCl) for example based on Mg, Zn, Cu, B, Si, Mn, Sn, Ge or Al. Particularly suitable M_2 include ZnCl, $(alkyl)_3Sn$, $(aryl)_3Sn$, $B(OR)_2$ (R is, eg, H or alkyl), MgBr, MgCl and MgI.

In a particularly preferred form of this aspect of the invention both M_1 and M_2 are derived from a Grignard reagent such as an alkyl magnesium halide eg. C_{1-4}alkylMgBr, (Cl) or (I). Suitable M_1 and M_2 thus include MgCl, MgBr and MgI.

Where X is NR in formula (I'), the nitrogen atom of the starting aniline is suitably protected by a nitrogen protecting group. Suitable nitrogen protecting groups are known to those skilled in the art of organic synthesis and include acyl groups (eg acetyl, trifluoroacetyl), phenyl, benzyl and benzoyl. Other suitable nitrogen protecting groups may be found in *Protective Groups in Organic Synthesis*, T. W. Greene and P. Wutz, John Wiley & Son, 3rd Edition.

The coupling agent used in step (a) of the process for the preparation is preferably a nickel or palladium based coupling agent. Suitable coupling agents are known in the art and include $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, Pd(dibenzylideneacetone)$_3$ and $PdCl_2(CH_3CN)_2$.

The leaving group of R_3-L can be any suitable leaving group known to the skilled person. In a preferred embodiment, where R_3 is an optionally substituted aryl, L can be a halogen such as iodine, chlorine or bromine, a triflate, or a sulfonate (eg tosylate, mesylate, brosylate nosylate etc).

Two preferred embodiments of the process for preparing compounds of formula (I') are schematically depicted in Figures 1 and 2.

The preparation of benzo[b]thiophenes of formula (I") is effected using a variation of the methods described for the benzo[b]furans and indoles of formula (I') above. In particular, the sulfur atom, X, must be protected by a suitable protecting group to circumvent competitive coupling of a thiolate to the aryl halide to afford xanthones. Suitable sulfur protecting groups are those which are capable of stabilizing a positive charge. Examples include benzyl, allyl, acetyls and thioacetals.

As used herein a Hal^+ producing agent is an agent which can effectively act as a Hal^+ source. Examples of Hal^+ producing agents include I_2, Br_2, Cl_2, IBr, Icl, chloroacetamide, iodoacetamide, N-chlorosuccinamide, N-bromosuccinamide and N-iodosuccinamide.

Suitable M_2 for compound (2) and coupling agents for the preparation of compounds of Formula (I") may include those described above.

The coupling of (4) with the moiety R_3-C(O)- or R_3- to produce (I") can be carried out via palladium-mediated coupling and/or metallation techniques as known in the art. For example, lithiation of (4) (eg using nBuLi) allows for coupling with R_3-C(O)-Hal (Hal is I, Br or Cl, preferably Cl). In another embodiment, Negishi coupling of (4) with R_3-ZnCl (derived from reaction of R_3-Li with ZnCl) gives access to compounds of formula (I") where A is a single bond. In another embodiment, palladium-mediated couplings such as Suzuki or Stille couplings can be used to access compounds of formula (I").

Some preferred embodiments for the preparation of Compounds of Formula (I") are shown in Figures 3, 4, 5 and 6.

In the preparation of compounds of Formula (I'"), step (b) involves the use of a metal hydride. Suitable metal hydrides are those which react with the triple bond to form an intermediate metallated vinyl group without reducing the adjacent carbonyl group and may include trialkylstannanes (eg trimethyl- or tributyl tin hydride), aryl stannanes (eg

triphenyl tin hydride), copper hydride, diisobutylaluminiumhydride, or borohydrides (eg catechol borane).

The cyclization step (d) employs acidic conditions, which can be either a H^+ source or a Lewis acid. Suitable acids include HCl, H_2SO_4, BF_3, $AlCl_3$, methanesulphonic acid etc. A preferred oxidizing agent is DDQ.

A schematic representation of one method for the preparation of compounds of Formula (I''') is depicted in Figure 7.

In the preparation of compounds of Formula (I''''), the coupling of (12) and (13) can be carried out using suitable metallation techniques known in the art. Thus the coupling can be carried out in the presence of n-BuLi sec-BuLi, t-BuLi or alkylMghalides such as iPrMgHalide

A schematic representation for a method of preparing compounds of Formula (I'''') is shown in Figure 8.

Compounds of Formula (II) can be prepared by coupling of a suitably protected thiol aldehyde under Negishi conditions, lithiation and coupling with the appropriate ZnCl acetylide. Cyclisation using a Hal+ producing agent, eg iodocyclization using I_2, affords access to Formula (II).

A schematic representation for a method of preparing compounds of Formula (II) is shown in Figure 9.

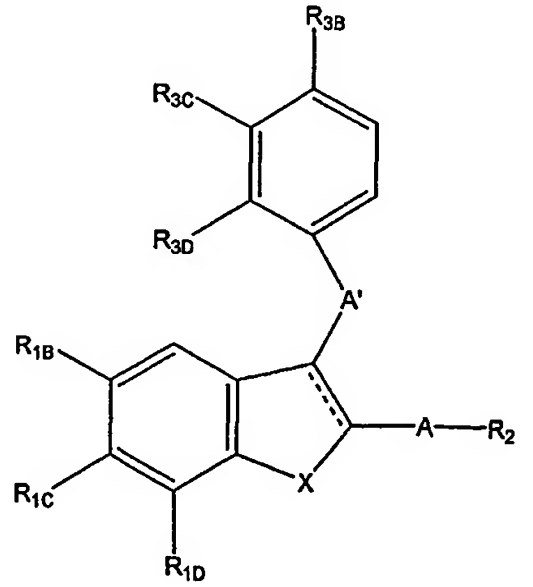
Compounds of Formula (III) can be prepared by palladium-mediated coupling of an appropriately protected butynyl sulfide with R_2-L, for example under Sonagashira conditions using CuI. Other palladium-mediated coupling procedures such as Stille, Suzuki, and Negishi conditions can also be used. Cyclization can be effected using a Hal+ producing agent as described herein. Coupling of the resulting Hal-dihydrothiophene with

an R_3 moiety, for example, using ZnCl-R_3, provides products where A' is a single bond. Alternatively, coupling with R_3-C(O)-Hal in the presence of nBuLi as described herein provides access to compounds of Formula (III) wherein A' is C=O, CH_2 or CH(OR').

A schematic representation for a method of preparing compounds of Formula III is depicted in Figure 10.

An important aspect of the present invention relates to compounds which may possess tubulin binding activity. Compounds which possess tubulin binding activity may act as anti-mitotic agents and may be effective in targeting tumour vasculature.

Thus, the invention also provides compounds of Formula (I'''')



(I'''')

wherein X is O, S, NR (wherein R is hydrogen, sulfonyl, C_{1-6}alkyl, C_{1-7}acyl or an aryl group) or C=O;
and ------ is an optional double bond;

R_{1B}-R_{1D} and R_{3B}-R_{3D} are independently selected from hydrogen, hydroxy, methoxy, and amino or any 2 adjacent R_{1B}-R_{1D} and R_{3B}-R_{3D} from a dioxolanyl group;

R_2 is an optionally substituted aryl, preferably an optionally substituted phenyl group of

formula (i) as herein described.

A and A' are independently selected from the group consisting of a single bond, C=O, CH_2, and CH(OR'), (R'is hydrogen, C_{1-6}alkyl or C_{1-7}acyl) provided that when one of A or A' is C=O, CH_2 or CH(OR'), then the other is a single bond; and provided that when X is S or NH, A is C=O, CH_2 or CH(OR');

with the proviso that when R_{1B} is methoxy, R_{1C} and R_{1D} are both H, A and A' are both a single bond, R_{3B}-R_{3D} are each methoxy and R_2 is 3,4-dioxolanylphenyl, then X is not NH; and that when R_{1B} is methoxy, R_{1C} is hydroxy, A and A' are both a single bond, R_{3B}-R_{3D} are each methoxy and R_2 is 3-hydroxy, 4-methoxyphenyl, then X is not O.

In a preferred form of (I''''), X is O, C=O or NR, more preferably O.

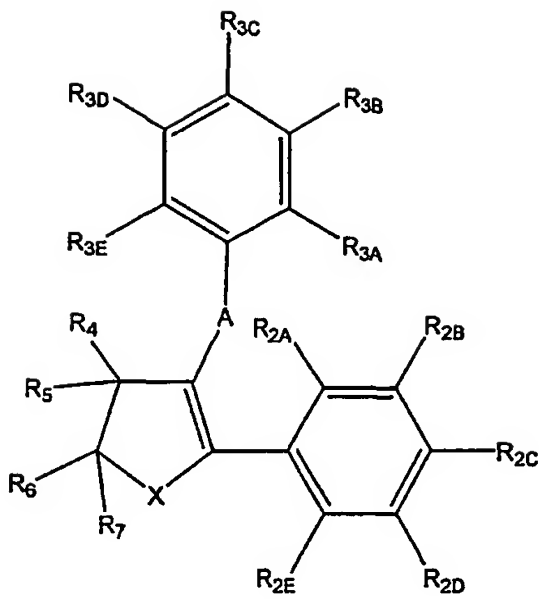
In another preferred form of (I'''') ------ is a double bond.

In another preferred embodiment of (I''''), when R_2 is a phenyl group of formula (i), at least one of R_{1B}-R_{1D} and R_{3B}-R_{3D} is a hydroxy or amino group which can be derivatized to form a salt or prodrug, such as an ester or amide, preferably a disodium phosphate ester .

In another preferred embodiment of (I''''), when R_2 is a phenyl group of formula (i), the phenyl group bears vicinal hydroxy and methoxy groups.

In another preferred embodiment of (I'''') at least one of A or A' is C=O, CH_2, CH(OR'). More preferably, when X is O, A' is C=O, CH_2 or CH(OR').

Yet other preferred compounds which may possess tubulin binding activity have the formula (IV):



(IV)

X is O, S or NR" (wherein R" is aryl, aroyl, acyl, benzyl, alkyl or sulfonyl)

A is a single bond C=O, CH(OR') (R' is hydrogen, C_{1-6}alkyl, C_{1-7}acyl), CH_2, O, S or NR (wherein R is hydrogen, C_{1-6} hydrogen, C_{1-6}alkyl or C_{1-7}acyl).

R_{2A}-R_{2E} and R_{3A}-R_{3E} are as hereinbefore described.

R_4-R_7 are independently selected from hydrogen, hydroxy, alkoxy, alkyl, amino, alkylamino, dialkylamino, acyl, acylamino and aryl, or R_4 and R_7 together form a bond.

The compounds of Formula (IV) can be prepared using iodocyclisation procedures known for forming compounds where X = O or N (Bev, S.P. et al. *Chem. Commun.* 1996, 1007 and Knight, D.W. et al. *Chem. Commun.* 1998, 2207) or for where X = S, analogous methodology as described herein.

Couplings of the aryl groups R_2 and R_3 can be performed as described herein and for where A is O, S or NH, see Bavanno, D., et al, *Curr. Org. Chem.* 1997, 3, 287 and references cited therein.

Some examples of compounds of the invention which possess tubulin-binding activity are depicted in Figure 11.

Certain compounds of the invention having tubulin binding activity or which have anti-tumour vasculature activity, may be useful in methods of therapy. In particular these compounds may be used for treating tumours. As used herein the term "tumour" is used to define any malignant cancerous growth, and may include leukemias, melanomas, colon, lung, ovarian, skin, breast, prostate, CNS, and renal cancers, as well as other cancers.

The compound of the invention having tublin binding activity may also be used in the treatment of solid tumours, eg. breast cancer.

The invention also provides for the use of a compound of formula (I"") or (II)-(IV) in the manufacture of a medicament for treating tumours.

There is also provided a method of treatment of solid tumours comprising the administration of an effective amount of a compound of formula (I"") or (II)-(IV) to a subject in need thereof.

The compounds of the invention may be particularly useful in combination therapy, eg. combining the treatment with other chemotherapeutic or radiation treatments.

However, it will be understood that the compounds of the invention can be used in the treatment of any disease for which tublin polymerization plays a crucial role.

Compounds of the invention which possess bioactivity, such as tubulin binding activity, can be formulated as a composition, particularly a pharmaceutical composition, together with a pharmaceutically acceptable additive.

The compounds of the invention are administered to the subject in a treatment effective amount. As used herein, a treatment effective amount is intended to include at least partially attaining the desired effect, or delaying the onset of, or inhibiting the

progression of, or halting or reversing altogether the onset or progression of the particular disease of condition being treated.

As used herein, the term "effective amount" relates to an amount of compound which, when administered according to a desired dosing regimen, provides the desired therapeutic activity. Dosing may occur at intervals of minutes, hours, days, weeks, months or years or continuously over any one of these periods. Suitable dosages lie within the range of about 0.1 ng per kg of body weight to 1 g per kg of body weight per dosage. The dosage is preferably in the range of 1 μg to 1 g per kg of body weight per dosage, such as is in the range of 1 mg to 1 g per kg of body weight per dosage. In one embodiment, the dosage is in the range of 1 mg to 500 mg per kg of body weight per dosage. In another embodiment, the dosage is in the range of 1 mg to 250 mg per kg of body weight per dosage. In yet another preferred embodiment, the dosage is in the range of 1 mg to 100 mg per kg of body weight per dosage, such as up to 50 mg per body weight per dosage.

Suitable dosage amounts and dosing regimens can be determined by the attending physician and may depend on the particular condition being treated, the severity of the condition as well as the general age, health and weight of the subject.

The active ingredient may be administered in a single dose or a series of doses. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a composition, preferably as a pharmaceutical composition. The formulation of such compositions is well known to those skilled in the art. The composition may contain any suitable carriers, diluents or excipients. These include all conventional solvents, dispersion media, fillers, solid carriers, coatings, antifungal and antibacterial agents, dermal penetration agents, surfactants, isotonic and absorption agents and the like. It will be understood that the compositions of the invention may also include other supplementary physiologically active agents.

The carrier must be pharmaceutically "acceptable" in the sense of being compatible with the other ingredients of the composition and not injurious to the subject.

Compositions include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parental (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g inert diluent, preservative disintegrant (e.g. sodium starch glycolate, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured base, usually sucrose and acacia or tragacanth gum; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia gum; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Compositions suitable for topical administration to the skin may comprise the compounds dissolved or suspended in any suitable carrier or base and may be in the form of lotions, gel, creams, pastes, ointments and the like. Suitable carriers include mineral oil, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. Transdermal patches may also be used to administer the compounds of the invention.

Compositions for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter, glycerin, gelatin or polyethylene glycol..

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Compositions suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bactericides and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection

solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage compositions are those containing a daily dose or unit, daily sub-dose, as herein above described, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the active ingredients particularly mentioned above, the compositions of this invention may include other agents conventional in the art having regard to the type of composition in question, for example, those suitable for oral administration may include such further agents as binders, sweeteners, thickeners, flavouring agents disintegrating agents, coating agents, preservatives, lubricants and/or time delay agents. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

The novel bioactive compounds of the invention can be administered to a subject as a salt or prodrug thereof. The term "salt, or prodrug" includes any pharmaceutically acceptable salt, ester, solvate, hydrate or any other compound which, upon administration to the recipient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since these may be useful in the preparation of pharmaceutically acceptable salts. Any compound that is a prodrug of a compound of formula (I) is within the scope and spirit of the invention. The term "pro-drug" is used in

its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, for example, compounds where a free hydroxy group is converted into an ester, such as an acetate or phosphate ester, or where a free amino group is converted into an amide. Procedures for esterifying, eg. acylating, the compounds of the invention are well known in the art and may include treatment of the compound with an appropriate carboxylic acid, anhydride or chloride in the presence of a suitable catalyst or base. A particularly preferred prodrug is a disodium phosphate ester. The disodium phosphate ester of novel compounds of the invention may be useful in targeting tumour vasculature and thus may provide a means of selective delivery of the compounds to the body. The disodium phosphate ester may be prepared in accordance with the methodology described in Pettit, G. R., *et al*, *Anticancer Drug Des.*, 1995, 10, 299.

Suitable pharmaceutically acceptable salts include, but are not limited to salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, maleic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluenesulphonic, benezenesulphonic, salicyclic sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium. In particular, the present invention includes within its scope cationic salts eg sodium or potassium salts, or alkyl esters (eg methyl, ethyl) of the phosphate group.

Basic nitrogen-containing groups may be quarternised with such agents as lower alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

The compounds of the invention may be in crystalline form either as the free compounds or as solvates (e.g. hydrates) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

It will also be recognised that compounds of the invention may possess asymmetric centres and are therefore capable of existing in more than one stereoisomeric form. The invention thus also relates to compounds in substantially pure isomeric form at one or more asymmetric centres eg., greater than about 90% ee, such as about 95% or 97% ee or greater than 99% ee, as well as mixtures, including racemic mixtures, thereof. Such isomers may be prepared by asymmetric synthesis, for example using chiral intermediates, or mixtures may be resolved by conventional methods, eg., chromatography, or use of a resolving agent.

The synthetic methods and processes described herein are amenable to combinatorial chemistry to produce libraries of compounds for biological screening.

Traditionally, drug candidates have been synthesized individually, this being a time consuming and laborious process if the synthetic sequence contains even just a few steps and large numbers of compounds are to be evaluated for their biological activity. Combinatorial synthesis is an emerging technique for effecting the generation of large libraries of molecules and has been successfully exploited in the synthesis and evaluation of small organic libraries. These libraries and their starting substrates may exist as molecules in free solution or preferably, linked to a solid phase, for example, beads, pins, microtitre plates (wells) or microchips which can be polymeric, glass, silica or other suitable substrate. Chemical diversity can be achieved by either parallel or split (split and mix) syntheses wherein each step has the potential to afford a multitude of compounds. Solution phase libraries may be prepared via parallel syntheses wherein different compounds are synthesised in separate reaction vessels in parallel, often in an automated fashion. Alternatively, attachment of the individual components employed in a synthetic sequence to an appropriate solid phase support allows for the further creation of chemical

diversity by utilizing not only parallel synthesis but also split synthesis wherein the solid support containing the compounds prepared in the prior step can be split into a number of batches, treated with the appropriate reagent and recombined.

The substrates can be attached to a solid support surface by any linkers known in the art. The linkers may be any component capable of being cleaved to release the substrate or final compound from the support.

Thus, libraries of compounds can be synthesized by initially attaching the first compound substrate to a solid support surface which can be performed by providing a plurality of solid support surfaces, suitably derivatizing each of the surfaces with groups capable of reacting with either the compound substrate or a linker moiety attached thereto. The various support surfaces with the attached first compound substrate can then be subjected to various reaction conditions and second compound substrates to provide a library of attached compounds, which may, if necessary, be reacted further with third and subsequent compound substrates or varying reactions conditions. Attachment and detachment of substrates and products can be performed under conditions similar to those as described in Johnson, M.G., *et al.*, *Tetrahedron*, 1999, 55, 11641; Han Y., *et al.* *Tetrahedron* 1999, 55, 11669; and Collini, M.D., *et al.*, *Tetrahedron Lett.*, 1997, 58, 7963.

Thus, the invention provides libraries of compounds of at least two compounds of Formula (I), (I')-(I''''), (II)-(IV) attached to a solid support surface or pluralities of surfaces.

Those skilled in the art will appreciate that the invention described herein in susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications which fall within the spirit and scope. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

Certain embodiments of the invention will now be described with reference to the

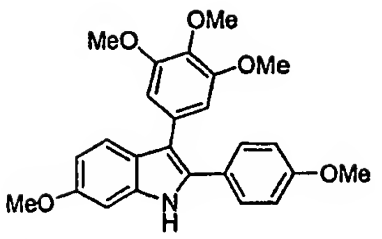
following examples which are intended for the purpose of illustration only and are not intended to limit the scope of the generality hereinbefore described.

EXAMPLES

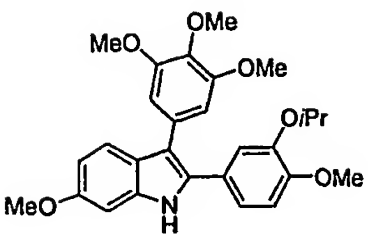
General methods:

Melting points were recorded with a Kofler hot-stage apparatus and are uncorrected. Proton (^{1}H) and (^{13}C) NMR spectra were recorded with a Varian Gemini 300 spectrometer operating at 300 MHz for proton and 75.5 MHz for carbon. All NMR spectra were recorded in (D)chloroform ($CDCl_3$) at 20 °C. The protonicities of the carbon atoms observed in the carbon NMR were determined using attached proton test (APT) experiments. Infrared spectra (IR) we obtained as KBr discs or as films on NaCl plates and were recorded on a Perkin-Elmer *Spectrum One* Fourier-transform infrared spectrophotometer. Low-resolution electron impact mass spectra (MS) were recorded at 70 eV on either a VG micromass 7070F instrument or a JEOL AX-505H mass spectrometer. High-resolution mass spectra (HRMS) were recorded on a VG micromass 7070F instrument. Elemental analyses were performed on a Carlo Erba 1106. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Flash chromatography was performed on Merk Kieselgel 60.

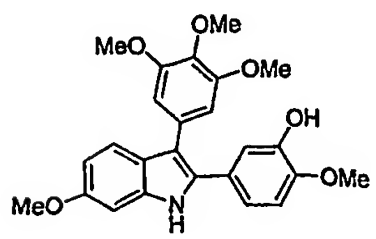
INDOLES



6-Methoxy-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)indole (BLF-36-1):
Methylmagnesium chloride (1.37 mL, 3.0 M in THF, 4.11 mmol) was added dropwise to a solution of 2-iodo-5-methoxyacetanilide (550 mg, 2.0 mmol) and 4-methoxyphenyl acetylene (276 mg, 2.1 mmol) in dried THF (5.0 mL) at –5 °C. The reaction mixture was then warmed to 18 °C, $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol) added and the reaction mixture heated to 65 °C for 0.5 h, after which time the reaction was shown to be complete by T.L.C.. The solution was cooled to 18 °C, diluted with DMSO (8.0 mL) and 3,4,5-trimethoxyiodobenzene (617 mg, 2.1 mmol) added. The solution heated to 80 °C (external temperature) and a slight flow of N_2(g) for 1 h (to remove THF) and heating continued under a stationary atmosphere of N_2(g) for a further 10 h. The reaction mixture was cooled to 18 °C diluted with ethyl acetate (150 mL) and washed with water (2x 100 mL) and brine (3x 100 mL), dried over $MgSO_4$ and concentrated onto silica gel (5 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, eluted sequentially with hexane / CH_2Cl_2 / diethyl ether 2:1:1 and 1:1:1). The relevant fractions (R_f = 0.328, CH_2Cl_2) were concentrated giving the product as a white solid (782 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 6.91-6.82 (m, 4H), 6.65 (s, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.74 (s, 6H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 158.9 (C), 156.6 (C), 153.1 (C), 136.4 (C), 136.2 (C), 132.8 (C), 130.9 (C), 129.2 (CH), 125.2 (C), 123.0 (C), 120.0 (CH), 113.9 (CH), 113.8 (C), 110.1 (CH), 106.8 (CH), 94.4 (CH), 60.9 (CH_3), 55.9 (2x CH_3), 55.7 (CH_3), 55.3 (CH_3). IR (KBr disc, cm^{-1}) 3368, 2999, 2933, 2831,1574, 1514, 1405, 1332, 1260, 1180, 1128. MS (70 eV) *m/z* (%): 419 (M^+, 100), 404 ($M^+ - CH_3$, 20).

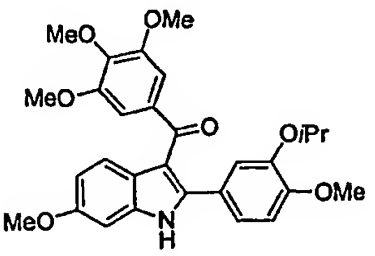


6-Methoxy-2-(3-isopropoxy-4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)indole: $Pd(PPh_3)_2Cl_2$ (11 mg, 0.015 mmol) and CuI (6.0 mg, 0.03 mmol) were added to a solution of triethylamine (140 μL, 1.0 mmol), 2-iodo-5-methoxytrifluoroacetanilide (173 mg, 0.50 mmol) and 3-isopropoxy-4-methoxyethynylbenzene (105 mg, 0.55 mmol) in dry acetonitrile (4.0 mL). The reaction mixture was stirred at 18 °C for 1 h, after which time the reaction was shown to be complete by TLC. K_2CO_3 (207 mg, 1.50 mmol) and 3,4,5-trimethoxyiodobenzene **7** (162 mg, 0.55 mmol) were added, and the reaction mixture was stirred at 18 °C for 18 h. After this time it was diluted with diethyl ether (50 mL), washed with H_2O (2 x 50 mL), dried over $MgSO_4$ and concentrated onto silica gel (1 g). The solid residue was subjected to flash chromatography (silica gel, hexane / CH_2Cl_2 / diethyl ether 3:3:1). The relevant fractions (R_f = 0.20, in eluant) were concentrated, giving the product as a white solid (183.2 mg, 77%) mp = 184-5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (br s, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.89 – 6.81 (m, 3H), 6.68 (s, 2H), 4.24 (septet, *J* = 6.0 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 6H), 3.75 (s, 6H), 1.20 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 156.5 (C), 153.1 (C), 149.5 (C), 146.8 (C), 136.3 (C), 136.1 (C), 132.8 (C), 131.1 (C), 125.3 (C), 123.1 (C), 119.8 (CH), 115.3 (CH), 113.7 (C), 111.6 (CH), 109.9 (CH), 106.9 (CH), 94.5 (CH), 71.1 (CH), 60.8 (CH_3), 55.9 (CH_3), 55.7 (CH_3), 55.6 (CH_3) 21.7 (CH_3) (2 x Ar CH superimposed). IR (KBr disc, cm^{-1}): 3404, 3000, 2930, 2834, 1573, 1496, 1462, 1317, 1249, 1212, 1124. MS (70 eV) *m/z* (%): 477 (M^+, 100), 463 ($M^+ - CH_3$, 13), 420 (12), 351 (20). HRMS calcd for $C_{28}H_{31}NO_6$: 477.2151. Found: 477.2158.



6-Methoxy-2-(3-hydroxy-4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)indole (BLF-61-3):

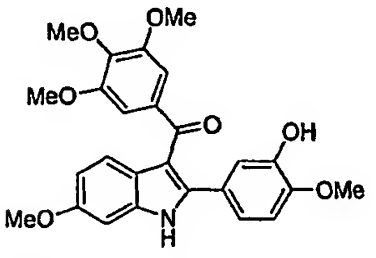
Aluminium trichloride (80.0 mg, 0.60 mmol) was added to a solution of isopropylether of **BLF-61-3** (above) (96.0 mg, 0.20 mmol) in dry dichloromethane (3 mL) and the reaction mixture stirred at 18 °C for 2 h. The solution was then diluted with NH_4Cl(aq) (sat., 20 mL) and extracted with ethyl acetate (2 x 15 mL). The combined ethyl acetate extracts were dried over $MgSO_4$ and concentrated onto silica gel (1 g). The solid residue was subjected to flash chromatography (silica gel, hexane / dichloromethane / diethyl ether 2:2:1), giving the product, **BLF-61-3**, as a white solid (81.0 mg, 93%) mp = 98-9 °C. ^{1}H NMR (300 MHz, D_6DMSO) δ 11.15 (s, 1H), 9.03 (s, 1H), 7.43 (d, J = 9.0 Hz, 1H), 6.89 (m_c, 4H), 6.68 (dd, J = 2.1, 9.0 Hz, 1H), 6.57 (s, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H), 3.64 (s, 6H). ^{13}C NMR + APT (75 MHz, D_6DMSO) δ 155.9 (C), 152.9 (C), 147.3 (C), 146.3 (C), 136.6 (C), 135.9 (C), 133.2 (C), 131.2 (C), 125.6 (C), 122.4 (C), 119.4 (CH), 115.6 (CH), 112.3 (C), 112.2 (CH), 109.7 (CH), 107.0 (CH), 94.5 (CH), 60.3 (CH_3), 55.8 (CH_3), 55.7 (CH_3), 55.4 (CH_3). IR (KBr disc, cm^{-1}): 3385, 2934, 2833, 1626, 1582, 1513, 1461, 1407, 1338, 1249, 1203, 1161, 1124. MS (70 eV) *m/z* (%): 435 (M^+, 100), 420 ($M^+ - CH_3$, 16). HRMS calcd for $C_{25}H_{25}NO_6$: 435.1682. Found: 435.1681.



6-Methoxy-2-(3-isopropoxy-4-methoxyphenyl)-3-(3,4,5-trimethoxybenzoyl)indole:

$Pd(PPh_3)_2Cl_2$ (11 mg, 0.015 mmol) and CuI (6.0 mg, 0.03 mmol) were added to a solution of triethylamine (140 μL, 1.0 mmol), 2-iodo-5-methoxytrifluoroacetanilide (173 mg, 0.50 mmol) and 3-isopropoxy-4-methoxyethynylbenzene (105 mg, 0.55 mmol) in dry acetonitrile (4.0 mL). The reaction mixture was stirred at 18 °C for 1 h, after which time the reaction was shown to be complete by TLC. K_2CO_3 (207 mg, 1.50 mmol) and 3,4,5-trimethoxyiodobenzene 7 (162 mg, 0.55 mmol) were added and the N_2 (g) atmosphere exchanged for carbon monoxide (1 atm, balloon). This reaction mixture was stirred at 18

°C for 18 h. After this time it was diluted with diethyl ether (50 mL), washed with H_2O (2 x 50 mL), dried over $MgSO_4$ and concentrated onto silica gel (1 g). The solid residue was subjected to flash chromatography (silica gel, hexane / CH_2Cl_2 / diethyl ether 2:4:1 and 1:1:2). The relevant fractions (R_f = 0.50, hexane / CH_2Cl_2 / diethyl ether 2:1:1) were concentrated, giving the product as a yellow solid (185.0 mg, 73%) mp = 196-7 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (br s, 1H), 7.93 (d, J = 9.0 Hz, 1H), 6.96 (s, 2H), 6.93 (m_c, 2H), 6.86 (d, J = 2.1 Hz, 1H), 6.73 (d, J = 1.8 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 4.10 (septet, J = 6.0 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.60 (6H), 1.13 (d, J = 6.0 Hz, 6H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 192.1 (C), 157.0 (C), 152.3 (C), 150.5 (C), 146.8 (C), 142.9 (C), 140.9 (C), 136.5 (C), 134.5 (C), 124.6 (C), 123.0 (C), 122.1 (CH), 121.1 (CH), 117.0 (CH), 112.1 (C), 111.5 (CH), 111.2 (CH), 107.1 (CH), 94.6 (CH), 71.5 (CH), 60.7 (CH_3), 55.7 (CH_3), 55.6 (CH_3), 55.4 (CH_3) 21.8 (CH_3). IR (KBr disc, cm^{-1}): 3344, 2939, 2835, 1614, 1575, 1541, 1492, 1459, 1420, 1335, 1256, 1203, 1125. MS (70 eV) *m/z* (%): 505 (M^+, 100), 463 ($M^+ - CH_3CH{=}CH_2$, 26), 308 (26), 218 (46). HRMS calcd for $C_{29}H_{31}NO_7$: 505.2101. Found: 505.2106.

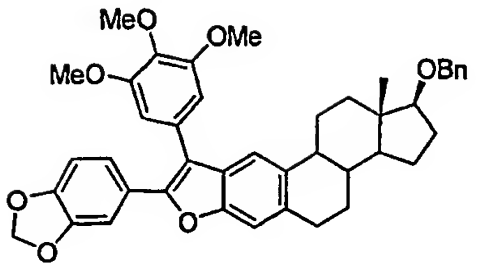


6-Methoxy-2-(3-hydroxy-4-methoxyphenyl)-3-(3,4,5-trimethoxybenzoyl)indole (BLF-67-3):

The isopropyl ether of **BLF-67-3** (above) was cleaved as described for **BLF-61-3** (above) (76.0 mg, 91%) mp = 189-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (br s, 1H), 7.85 (d, J = 9.3 Hz, 1H), 6.94 (s, 2H), 6.88 (m, 3H), 6.70 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 6.50 (d, J = 8.4Hz), 1H), (d, J = 8.7 Hz, 1H), 6.95 (d, J = 1.5 Hz, 1H), 6.88-6.82 (m, 3H), 5.69 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.67 (s, 6H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 192.5 (C), 156.9 (C), 152.3 (C), 146.9 (C), 145.2 (C), 143.1 (C), 140.8 (C), 136.4 (C), 134.9 (C), 124.9 (C), 122.8 (C), 122.0 (CH), 121.4 (CH), 114.9 (CH), 112.4 (C), 107.1 (CH), 94.5 (CH), 60.7 (CH_3), 55.9 (2x CH_3), 55.7 (CH_3), 55.5 (CH_3). IR (KBr disc, cm^{-1})

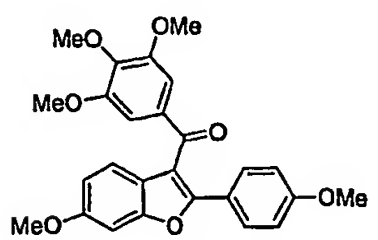
3420, 3322, 2937, 2836, 1626, 1579, 1496, 1455, 1419, 1345, 1321, 1261, 1228, 1199, 1127. MS (70 eV) *m/z* (%): 463 ($M^{+\cdot}$, 100), 448 ($M^{+\cdot} - CH_3$, 10). HRMS calcd for $C_{25}H_{25}NO_7$ 463.1631. Found 463.1648.

BENZOFURANS AND BENZOPYRANS



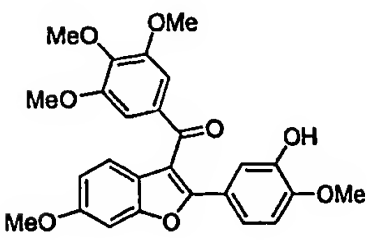
2,3-[2'-(3",4"-methylenedioxyphenyl)-3'-(3"',4"',5"'-trimethoxyphenyl)furano]-17-*O*-benzylestradiol:

This product was prepared as described for **BLF-36-1** using 2-iodo-17-*O*-benzylestradiol (270 mg, 0.55 mmol), 3,4-(methylenedioxy)phenylacetylene (104 mg, 0.71 mmol) and 3,4,5-trimethoxyiodobenzene (211 mg, 0.72 mmol) giving white solid product (70% yield) ^{1}H-NMR ($CDCl_3$) δ 7.39 (s, 1H, Ar-H), 7.30 (m, 5H, Ar-H), 7.25 (s, 1H, Ar-H), 7.21 (dd, *J* = 8.1 Hz and 1.8 Hz, 1H, Ar-H), 7.16 (d, *J* = 1.8 Hz, 1H, Ar-H), 6.78 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.70 (s, 2H, Ar-H), 5.98 (s, 2H, O-CH_2-O), 4.59 (s, 2H, Ph-CH_2), 3.97 (s, 3H, OCH_3), 3.83 (s, 6H, 2x OCH_3), 3.53 (t, *J* = 7.8 Hz, 1H, CH), 3.02 (m, 1H), 2.35 – 0.89 (17H). ^{13}C-NMR ($CDCl_3$) δ 153.8, 152.3, 149.7, 147.7, 147.6 (C-O), 139.4, 137.4, 135.9, 134.4, 130.7, 128.7 (Ar-C), 128.3 (2 x Ar-CH), 127.4 (3 x ArCH), 124.9 (Ar-C), 121.2 (Ar-CH), 116.4 (Ar-C), 115.9, 110.5 , 108.5, 107.3 (Ar-C), 106.7 (2 x Ar-C), 101.3 (O-CH_2-O), 88.3 (CH-O-Bn), 71.7 (Ph-CH_2), 61.1 (OCH_3), 56.3 (2 x OCH_3), 50.5, 44.5, (CH) 43.4 (CH_2), 38.7 (CH), 38.0, 30.2, 28.1, 27.4, 26.7, 23.3 (CH_2), 11.9 (CH_3). LRMS m/z = 672 (100) ($M^{+\cdot}$), 91 (26) ($C_7H_7^+$).HRMS Calculated = 672.308704. Found = 672.309253. IR (neat) ν max = 2932, 1580, 1505, 1489, 1465, 1453, 1411, 1379, 1299, 1236, 1128, 1105, 1038, 736.



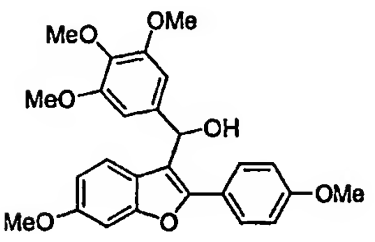
6-Methoxy-2-(4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)benzo[*b*]furan (BLF-28-1):

Methylmagnesium chloride (1.40 mL, 3.0 M in THF, 4.2 mmol) was added dropwise to a solution of 2-iodo-5-methoxyphenol (500 mg, 2.0 mmol) and 4-methoxyphenyl acetylene (290 mg, 2.2 mmol) in dried THF (5.0 mL) at –5 °C. The reaction mixture was then warmed to 18 °C, $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol) added and the reaction mixture heated to 65 °C for 1 h, after which time the reaction was shown to be complete by T.L.C.. The THF was removed by passing a steady flow of N_2 (g) over the heated solution. This was cooled to 18 °C and DMSO (8.0 mL) added and the N_2(g) atmosphere exchanged for carbon monoxide (1 atm.) and stirred for 0.3 h. After this time 3,4,5-trimethoxyiodobenzene (624 mg, 2.12 mmol) was added and the solution heated to 80 °C (external temperature) for 16 h. The reaction mixture was cooled to 18 °C diluted with ethyl acetate (100 mL) and washed with water (2x 80 mL) and brine (3x 80 mL), dried over $MgSO_4$ and concentrated onto silica gel (3 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, eluted sequentially with hexane / CH_2Cl_2 2:1, 1:1, 1:2). The relevant fraction (R_f = 0.23, hexane / diethyl ether 2:1) were concentrated giving the product as a yellow solid (510 mg, 58%), mp = 108-9 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 8.7 Hz, 1H), 7.13 (s, 2H), 7.09 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 2.4 Hz, 8.7 Hz, 1H), 6.82 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.70 (s, 6H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 190.4 (C), 160.2 (C), 158.2 (C), 156.9 (C), 154.4 (C), 152.5 (C), 142.0 (C), 132.3 (C), 129.5 (CH), 122.0 (C), 121.5 (C), 121.4 (CH), 114.2 (C), 113.5 (CH), 112.3 (CH), 107.0 (CH), 95.2 (CH), 60.6 (CH_3), 55.7 (2x CH_3), 55.3 (CH_3), 54.9 (CH_3). IR (KBr disc, cm^{-1}) 2935, 2833, 1647, 1609, 1584, 1494, 1455, 1438, 1409, 1368, 1304, 1254. MS (70 eV) *m/z* (%): 448 ($M^{+\cdot}$, 100), 433 ($M^{+\cdot} - CH_3$, 15). HRMS calcd for $C_{26}H_{24}O_7$ 448.1522. Found 448.1520.



6-Methoxy-2-(3-hydroxy-4-methoxyphenyl)-3-(3,4,5-trimethoxybenzoyl)benzo[*b*]furan (BLF-62-3)

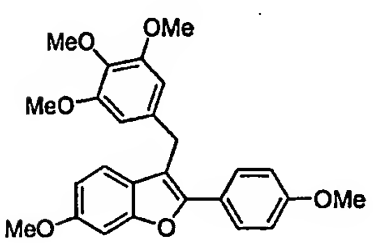
The isopropyl ether of **BLF-62-3** was prepared using an identical procedure as that described above for **BLF-28-1** and the isopropyl ether group cleaved as described for **BLF-61-3** above (60 % over both steps). **BLF-62-3**: mp = 68-9 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.7 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.13 (s, 2H), 7.10-7.05 (m, 2H), 6.91 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 5.64 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.71 (s, 6H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 190.9 (C), 158.4 (C), 156.9 (C), 154.6 (C), 152.7 (C), 147.6 (C), 145.4(C), 142.2 (C), 132.6 (C), 123.0 (C), 121.8 (C), 121.6 (CH), 121.1 (CH), 114.8 (C), 114.1 (CH), 112.6 (CH), 110.2 (CH), 107.2 (CH), 95.5 (CH), 60.8 (CH_3), 56.0 (2x CH_3), 55.8 (CH_3), 55.7 (CH_3). IR (KBr disc, cm^{-1}) 3400, 2940, 2837, 1622, 1581, 1494, 1462, 1414, 1262, 1232, 1126. MS (70 eV) *m/z* (%): 464 (M^+, 100), 449 ($M^+ - CH_3$, 10), 408.2 (15) HRMS calcd for $C_{26}H_{24}O_8$ 464.1471. Found 464.1459.



6-Methoxy-2-(4-methoxyphenyl)-3-[α-hydroxy-α-(3,4,5-trimethoxyphenyl)methyl]benzo[*b*]furan (BLF-68-3):

Sodium borohydride (15.0 mg, 0.40 mmol) was added to a solution of **BLF-28-1** (155 mg, 0.35 mmol) in ethanol (3 mL) and the solution stirred at 18 °C for 1 h. The reaction mixture was then diluted with HCl (aq) (1% w/v, 15 mL) and the product extracted with ethyl acetate (2x 15 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the product as a white solid. This material was suspended in a diethyl ether (3 mL) and filtered giving the pure product as a white solid: mp = 53-4 °C. ^{1}H NMR (300 MHz, D_6Acetone) δ 7.77 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 1H), 7.10-7.05 (m, 3H), 6.81 (s, 2H), 6.74 (dd, J = 2.4, 8.7 Hz, 1H), 6.20 (d, J = 4.2 Hz, 1H), 5.09 (d,

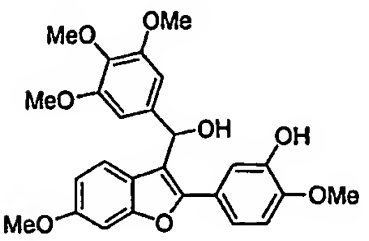
J = 4.2 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.70 (s, 6H), 3.68 (s, 3H). ^{13}C NMR + APT (75 MHz, D_6Acetone) δ 160.9 (C), 158.9 (C), 155.9 (C), 154.1 (C), 152.1 (C), 140.1 (C), 138.9 (C), 129.7 (CH), 124.2 (C), 122.9 (CH), 122.5 (C), 118.5 (C), 115.0 (CH), 112.1 (CH), 104.4 (CH), 96.1 (CH), 68.6 (CH), 60.5 (CH_3), 56.3 (CH_3), 55.9 (CH_3), 55.7 (CH_3). IR (KBr disc, cm^{-1}): 3467, 2936, 2835, 1621, 1592, 1506, 1492, 1461, 1416, 1251, 1150, 1126. MS (70 eV) *m/z* (%): 450 (M^+, 100), 281 (11), 149 (16). HRMS calcd for $C_{26}H_{26}O_7$: 450.1679. Found: 450.1677.



6-Methoxy-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxybenzyl)benzo[*b*]furan (BLF-70-3):

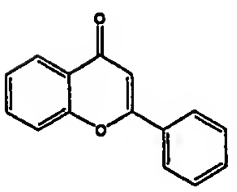
The procedure described above to produce **BLF-68-3** was repeated (same scale) and the crude product obtained from extraction with ethyl acetate. The crude product was dissolved in $CHCl_3$ (3 mL) and triethylsilane (200 μL) and trifluoroacetic acid (300 μL) added and the reaction mixture stirred at 45 °C for 1 h. This solution was then cooled to room temperature, diluted with diethyl ether (30 mL) and $NaHCO_3$(aq) (sat., 30 mL) added slowly to the swirled solution (gas evolution!). The organic phase was dried over $MgSO_4$ and concentrated onto silica (1 g) under reduced pressure. The solid residue was subject to flash chromatography (silca gel, sequential elution with hexane / CH_2Cl_2 2:1, 1:1) giving the product as a white solid: mp = 121-2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.7 Hz, 1H), 7.09 (d, J = 3.0 Hz, 1H), 6.98 (d, J = 8.7 Hz, 2H), 6.72 (dd, J = 3.0 Hz, 8.7 Hz, 1H), 6.49 (s, 2H), 4.14 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.75 (s, 6H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 159.4 (C), 157.9 (C), 154.8 (C), 153.3 (C), 151.4 (C), 136.3 (C), 135.2 (C), 127.9 (CH), 123.9 (C), 123.7 (C), 119.7 (CH), 114.2 (CH), 112.0 (C), 111.3 (CH), 104.9 (CH), 95.7 (CH), 60.8 (CH_3), 56.0 (2x CH_3), 55.7 (CH_3), 55.3 (CH_3), 30.3 (CH_2). IR (KBr disc, cm^{-1}) 2935, 2835, 1613, 1587, 1491,

1506, 1460, 1437, 1330, 1243, 1181, 1163, 1138. MS (70 eV) *m/z* (%): 434 (M^+, 100), 419 ($M^+ - CH_3$, 11). HRMS calcd for $C_{26}H_{26}O_6$ 434.1729. Found 434.1740.



6-Methoxy-2-(3-hydroxy-4-methoxyphenyl)-3-[α-hydroxy-α-(3,4,5-trimethoxyphenyl)methyl]benzo[*b*]furan (BLF-69-3):

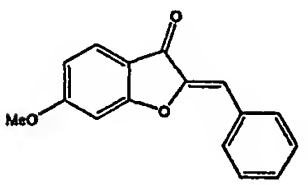
This product was prepared in a similar fashion to **BLF-68-3** using **BLF-62-3** (95 mg, 0.2 mmol) and sodium borohydride (33 mg, 1.0 mmol). The product was obtained as a white solid (90 mg, 94%): mp = 68-9 °C ^{1}H NMR (300 MHz, d_6Acetone) δ 8.00 (s, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.28 (dd, J = 2.1 Hz, 8.7 Hz, 1H), 7.07 (m, 2H), 6.82 (s, 1H), 6.73 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 6.21 (d, J = 4.5 Hz, 1H), 5.08 (d, J = 4.5 Hz, 1H), 389 (s, 3H), 3.82 (s, 3H), 3.71 (s, 6H), 3.68 (s, 3H). ^{13}C NMR + APT (75 MHz, d_6Acetone) δ 158.8 (C), 155.8 (C), 154.1 (C), 152.1 (C), 148.9 (C), 147.6 (C), 138.0(C), 124.7(C), 123.0 (CH), 122,4 (C), 120.0 (CH), 118.6 (C), 115.0 (CH), 112.5 (CH), 112.0 (C), 104.4 (CH), 96.1 (CH), 68.6 (CH), 60.4 (CH_3), 56.3 (3x CH_3), 55.8 (CH_3). IR (KBr disc, cm^{-1}) 3435, 2936, 2836, 1623, 1591, 1507, 1493, 1461, 1260, 1232, 1125. MS (70 eV) *m/z* (%): 466 (M^+, 100), 448 ($M^+ - H_2O$, 18), 408 (98). HRMS calcd for $C_{26}H_{26}O_8$ 466.1628. Found 466.1630.



2-Phenylbenzo[*b*]pyran-4-one.

n-Butyllithium (0.56 mL, 1.0 mmol) was added to a solution of 2-iodophenol (109.9 mg, 0.500 mmol) in THF (2 mL) at ⁻78°C (dry-ice / acetone bath). After 0.1 h, 3-

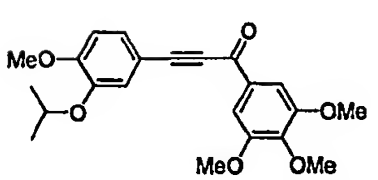
phenylpropynoyl chloride (82.2 mg, 0.500 mmol) was added, and the reaction warmed to room temperature. After 1 h, DMSO (4 mL) and water (0.5 mL) were added. After further stirring for 1 h, the solution was diluted with diethyl ether (50 mL), washed with $NH_4Cl_{(aq)}$ (10%, 40 mL), water (40 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexane / diethyl ether 95:5, 4:1, then 1:1) to give the product as a white solid (86 mg, 78%).



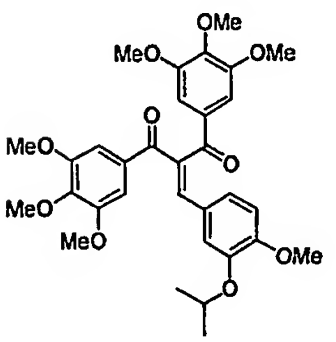
2-benzylidene-6-methoxybenzo[*b*]furan-3-one

n-Butyllithium (0.86 mL, 1.72 mmol) was added to a solution of 2-iodo-5-methoxyphenol (200 mg, 0.858 mmol) in THF (4 mL) at ⁻78°C (dry-ice / acetone bath). After 0.15 h, 3-phenylpropynoyl chloride (142 mg, 0.858 mmol) was added, and the reaction warmed to room temperature and quenched with $NH_4Cl_{(aq)}$ (10%, 30 mL). The solution was extracted with diethyl ether (3 x 50 mL), and concentrated under reduced pressure to give a brown residue. The residue was diluted with methanol (6 mL), and $AgNO_3$ (90 mg, 0.515 mmol) added, and the solution stirred for 2 h. After this time, the solution was diluted with diethyl ether (50 mL), washed with water (40 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexane / diethyl ether 9:1, 5:1, then 1:1) to give the product as a white solid (159, 74%).

INDANONES AND INDENONES

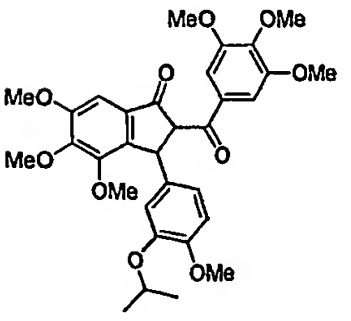


3-(3'-Isopropoxy-4'-methoxyphenyl)-1-(3'',4'',5''-trimethoxyphenyl)propyn-1-one.
n-Butyllithium (9.4 mL, 2.00 M in hexanes, 19 mmol) was added dropwise to a solution *β,β*-dibromo-3-isopropoxy-4-methoxystyrene (3.29 g, 9.39 mmol) in dry THF (50 mL) at –78 °C (dry ice/acetone) (produces lithium 3-isopropoxy-4-methoxyphenylacetylide). The solution was then allowed to return to room temperature before being again cooled to –78 °C. 3,4,5-Trimethoxybenzoyl chloride [2.27 g, 9.86 mmol, dissolved in THF (20 mL)] was added and the solution once again allowed to warm to room temperature. The reaction mixture was diluted with diethyl ether (100 mL), washed with distilled water (2 × 50 mL), dried over $MgSO_4$ and concentrated onto silica gel (1.5 g) under reduced pressure. The solid residue was subject to flash chromatography (silica gel, 2% ether in dichloromethane) giving a white solid (2.27 g, 65.7%), mp =130-31°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 2H, Ar-H), 7.28 (dd, *J* = 8.3Hz, 1.8Hz, 1H, Ar-H), 7.16 (d, *J* = 1.8Hz, 1H, Ar-H), 6.89 (d, *J* = 8.3Hz, 1H, Ar-H), 4.54 (m, *J* = 6.1Hz, 1H, *i*-Pr), 3.96 (s, 6H, OMe), 3.94 (s, 3H, OMe), 3.90 (s, 3H, OMe), 1.38 (d, 6H, *J* = 6.1Hz, *i*-Pr).^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 176.8 (C), 153.0 (C), 152.9 (C), 147.1 (C), 143.3 (C), 132.3 (C,), 127.3 (CH), 119.3 (CH), 111.7 (C), 111.6 (CH), 106.7 (CH), 94.4 (C), 86.3.4 (C), 71.6 (CH), 61.0 (CH_3), 56.2 (CH_3), 56.0 (CH_3), 21.9 (CH_3). IR (KBr disc, cm^{-1}) 3011, 2976, 2938, 2838, 2187, 1637, 1586, 1510, 1460, 1414. MS (70 eV) *m/z* (%): 384.1(M^+), 342.0, 299.0, 175.0



2-(3'-Isopropoxy-4'-methoxybenzylidine)-1,3-bis-(3'',4'',5''-trimethoxyphenyl)propan-1,3-dione.
Bis(dibenzylidineacetone)palladium (16 mg, 0.03 mmol) and triphenylphosphine (30 mg, 0.12 mmol) were dissolved in dry tetrahydrofuran (8 mL) under N_2 and stirred until the solution changed from red to yellow/orange (approximately 1 h). To this solution was added 1,3-diarylpropynone above (0.384g, 1.00 mmol), followed by dropwise addition of

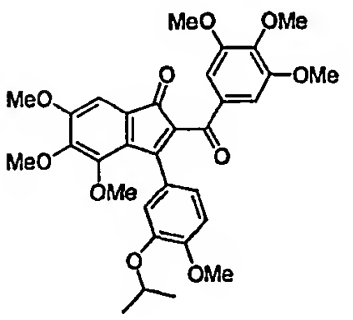
tributyltin hydride (0.28 mL, 1.0 mmol). The solution was then allowed to stir until TLC indicated complete reaction of the starting alkyne (approximately 0.5 h), after this time 3,4,5-trimethoxybenzoyl chloride (0.242 g, 1.05 mmol) and cuprous chloride (0.08 g, 0.80 mmol) were added. The solution was then stirred until TLC revealed complete consumption of the 3,4,5-trimethoxybenzoyl chloride (approximately 3 h). After this time the THF solution was taken up in diethyl ether (100 mL) and washed with aqueous KF solution (30%, 3 × 50 mL). The organic phase was then dried over $MgSO_4$ and concentrated onto silica gel (1 g) under reduced pressure. The solid residue was subject to flash chromatography (silica gel, 4% diethyl ether in dichloromethane) giving a light yellow solid (0.475 g, 81.7%), mp = 105-6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H, C=C-H), 7.28 (s, 2H, Ar-H), 7.10 (s, 2H, Ar-H), 6.97 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar-H), 6.86 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.78 (d, *J* = 8.5 Hz, 1H, Ar-H), 4.19 (m, *J* = 6.1 Hz, 1H, *i*-Pr), 3.91 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.83 (s, 9H, OMe), 3.80 (s, 6H, OMe), 1.18 (d, *J* = 6.1Hz, 6H, *i*-Pr).).^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 196.0 (C), 193.4 (C), 153.2 (C), 152.9 (C), 152.4 (C), 147.1 (C), 143.3 (CH), 143.2 (C), 141.8 (C), 136.7 (C), 132.6 (C), 131.3 (C), 125.7 (C), 125.2 (CH), 116.0 (CH), 111.3 (CH), 106.8 (CH), 106.7(CH), 71.3 (CH), 60.9 (CH_3), 56.1 (CH_3), 55.8 (CH_3), 21.7 (CH_3). IR (KBr disc, cm^{-1}) 2971, 2940, 2836, 1646, 1578, 1504, 1122, 998. MS (70 eV) *m/z* (%): 580.1(M^+), 385.1, 327.0, 195.0, 152.0, 77.0.



3-(3'-isopropoxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3'',4'',5''-trimethoxybenzoyl)-1-indanone.

1,3-Propadione above (0.581 g, 1.00 mmol) was dissolved in dry dichloromethane (20 mL), to this solution was added methanesulfonic acid (68 μL, 1.0 mmol). After 1 h stirring

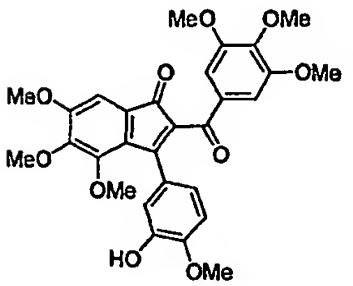
at room temperature the solution was taken up in diethyl ether (50 mL) and washed with distilled water (2 × 20 mL), the organic phase was then dried over $MgSO_4$ and the solvent removed under reduced pressure, a light yellow solid was returned (0.576g, 99.1%), mp = 65-6 °C. The ^{1}H NMR spectrum of this compound indicates the presence of an equilibrium mixture of the *trans*-isomer and an enol tautomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s), 7.19 (s), 7.05 (s), 6.83 (s) , 6.79 (d), 6.68 (dd), 6.67 (s), 6.64 (d), 6.61 (s), 6.56 (d), 5.14 (s), 4.99 (d, J = 2.5 Hz), 4.57 (d, J = 2.5 Hz), 4.42 (m), 4.29 (m), 3.71-3.95 (10 singlets), 3.45 (s), 3.32 (s), 1.31 (d), 1.26 (d), 1.20 (d), 1.18 (d).MS (70 eV) *m/z* (%): 580.1(M^+), 385.1, 343.0, 195.0. IR (KBr disc, cm^{-1}) 2972 m, 2937 m, 2835 w, 1714 m, 1667 m, 1583 s, 1505 s, 1336 s, 1125 vs



3-(3'-isopropoxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3'',4'',5''-trimethoxybenzoyl)indenone.

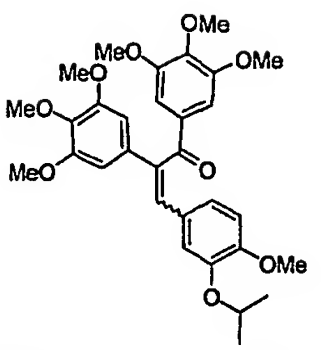
Indanone above (0.232 g, 0.40 mmol) and 2,3-dichloro-5,6-dicyanoquinone (0.136 g, 0.60 mmol) were dissolved in dry 1,2-dichloroethane (5 mL) and stirred at 60 °C for 3 days. After this time the solution was decanted from the precipitate (dihydro-DDQ), concentrated onto silica gel (0.5 g) and chromatographed (2:2:1 hexanes / dichloromethane / diethyl ether) to return a bright orange solid (185 mg, 80.1%), mp = 170-171 °C. ^{1}H NMR (300 MHz, $CDCl_3$)δ 7.16 (dd, J = 8.4, 2.1 Hz, 1H, Ar-H), 7.11 (s, 1H, Ar-H), 7.03 (s, 2H, Ar-H), 7.02 (d, J = 2.1 Hz, 1H, Ar-H), 6.76 (d, J = 8.4 Hz, 1H, Ar-H), 4.35 (m, J = 6.1 Hz, 1H, *i*-Pr), 3.94 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.77 (s, 6H, OMe), 3.39 (s, 3H, OMe), 1.25 (d, J= 6.1 Hz, 6H, *i*-Pr). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 192.1 (C), 191.2 (C), 161.8 (C), 155.5 (C), 152.7 (C), 152.1 (C), 150.6 (C), 147.4 (C), 146.3 (C), 142.7 (C), 131.8 (C), 131.4 (C), 127.4 (C), 126.2, 125.0 (C), 122.2 (CH), 116.0 (CH), 110.5 (CH), 106.9 (CH), 105.0 (CH), 71.5 (CH), 61.6 (CH_3),

61.2 (CH_3), 60.8 (CH_3), 56.5 (CH_3), 56.1 (CH_3), 55.8 (CH_3), 21.9 (CH_3). IR (KBr disc, cm^{-1}) 3001, 2974, 2937, 2839, 1709, 1641, 1600, 1583,1507, 1460, 1416. MS (70 eV) *m/z* (%): 578.0(M^+), 534.9, 368.9, 195.0



3-(3'-Hydroxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3'',4'',5''-trimethoxybenzoyl)indenone (DK-12a-1).

Indenone above (101 mg, 0.175 mmol) was dissolved in 5mL of dry dichloromethane, to this solution was added aluminium trichloride (94 mg, 0.700 mmol). After stirring for 0.15 h the mixture was taken up in diethyl ether (20 mL) and washed with aqueous ammonium chloride solution (10%, 2 × 30 mL), and water (20 mL). The organic phase was dried over $MgSO_4$ and evaporated onto silica gel (0.5g) under reduced pressure. The solid residue was subject to flash chromatography (silca gel, 7% diethyl ether in dichloromethane) giving an orange solid (71.4 mg, 76.1%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 2.1 Hz, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 7.01 (s, 2H, Ar-H), 6.96 (dd, J = 7.8, 2.1 Hz, 1H, Ar-H), 6.67 (d, J = 7.8 Hz, 1H, Ar-H), 5.57 (s, 1H, OH), 3.94 (s, 3H, Ome), 3.91 (s, 3H, Ome), 3.85 (s, 3H, Ome), 3.84 (s, 3H, Ome), 3.79 (s, 6H, Ome), 3.48 (s, 3H, Ome). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 192.1 (C), 191.0 (C), 162.1 (C), 155.7 (C), 152.7 (C), 150.7 (C), 148.1 (C), 147.4 (C), 144.8 (C), 142.5 (C), 132.0 (C), 131.5 (C), 127.3 (C), 126.2, 126.0 (C), 121.1 (CH), 114.7 (CH), 109.5 (CH), 106.8 (CH), 104.9 (CH), 61.4 (CH_3), 61.2 (CH_3), 60.8 (CH_3), 56.6 (CH_3), 56.1 (CH_3), 55.8 (CH_3). IR (KBr disc, cm^{-1}) 3418, 2934, 2840, 1707, 1641, 1606, 1581, 1504, 1465, 1411, 1362, 1339, 1124. MS (70 eV) *m/z* (%): 536.0(M+),493.0, 369.0, 343.0, 277.0, 219.0, 195.0



3-(3'-Isopropoxy-4'methoxyphenyl)-1,2-bis(3'',4'',5''-trimethoxyphenyl)propen-1-one :

Bis(dibenzylidineacetone)palladium (13 mg, 0.024 mmol) and triphenylphosphine (24 mg, 0.10 mmol) were dissolved in dry tetrahydrofuran (8 mL)under N_2 and stirred until the solution changed from red to yellow/orange (approximately 1 h). To this solution was added propynone above (0.307 g, 0.800 mmol), followed by dropwise addition of tributyltin hydride (97% solution, 0.22 mL, 0.800 mmol). The solution was then allowed to stir for 5 hours, after this time 3,4,5-trimethoxyiodobenene (0.194 g, 0.84 mmol) and cuprous chloride (0.16 g, 1.6 mmol) were added. The solution was then stirred until TLC revealed complete consumption of the 3,4,5-trimethoxyiodobenzene (3 days). After this time the THF solution was taken up in diethyl ether (100 mL) and washed with aqueous KF solution (30%, 3 × 50 mL). The organic phase was then dried over $MgSO_4$ and evaporated under reduced pressure onto silica gel (1 g). Flash chromatography (sequential elution 2% / 4% diethyl ether in dichloromethane) returned two isomers (higher R_f, 0.024 g, 5.4% / lower R_f, 0.105 g, 23.7%).

Higher R_f isomer

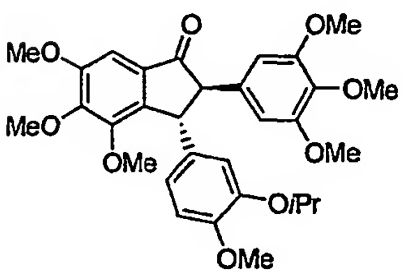
^{1}H NMR; δ 7.31 (s, 2H, Ar), 7.04 (s, 1H, C=C-H), 6.87 (dd, J = 8.2, 2.1Hz, 1H, Ar), 6.79 (d, J = 2.1Hz, 1H, Ar), 6.73 (d, J = 8.2, Hz, 1H, Ar), 6.64 (s, 2H, Ar), 4.22 (m, J = 6.1 Hz, 1H, *i*-Pr), 3.88 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.84 (s, 6H, OMe), 3.80 (s, 9H, 2 × OMe), 1.20 (d, J = 6.1 Hz, 6H, *i*-Pr).

Lower R_f isomer

^{1}H NMR; δ 7.26 (s, 1H, C=C-H), 7.09 (s, 2H, Ar), 6.83 (dd, J = 8.4, 2.1 Hz, 1H, Ar), 6.76 (d, J = 8.4 Hz, 1H, Ar), 6.63 (d, J = 2.1, Hz, 1H, Ar), 6.51 (s, 2H, Ar), 4.04 (m, J = 6.1 Hz, 1H, *i*-Pr), 3.92 (s, 3H, OMe), 3.86 (s, 9H, 2 × OMe), 3.83 (s, 3H, OMe), 3.77 (s, 6H, OMe), 1.18 (d, J = 6.1 Hz, 6H, *i*-Pr).

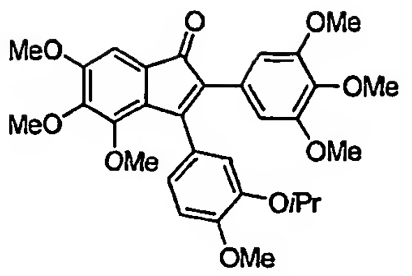
APT ^{13}C NMR: δ 196.0 (C), 153.7 (C), 152.7 (C), 151.3 (C), 146.6 (C), 141.4 (C), 141.1 (CH), 137.8 (C), 137.4 (C), 133.3 (C), 132.6 (C), 127.0 (C), 125.4 (CH), 115.6 (CH), 110.9 (CH), 107.1 (CH), 106.4 (CH), 70.8 (CH), 60.8 (CH_3), 60.7 (CH_3), 56.2 (CH_3), 56.0 (CH_3), 55.7 (CH_3), 21.7 (CH_3).

LRMS: *m/z* 552.2 (M^+), 509.2, 479.2, 345.1, 303.1, 269.0, 195.0



(±)*trans*-3-(3'-Isopropoxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3'',4'',5''-trimethoxyphenyl)-1-indanone:

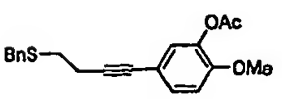
Prepared from 3-(3'-isopropoxy-4'methoxyphenyl)-1,2-bis(3'',4'',5''-trimethoxyphenyl)propen-1-one (above) in a similar manner as described for 3-(3'-isopropoxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3'',4'',5''-trimethoxybenzoyl)-1-indanone (above), giving the product as tan solid (80.8 mg, 81.0%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H, Ar), 6.79 (d, *J* = 8.0 Hz, 1H, Ar), 6.63 (dd, *J* = 8.0, 2.1 Hz, 1H, Ar), 6.61 (d, *J* = 2.1 Hz, 1H, Ar), 6.24 (s, 2H, Ar), 4.41 (m, *J* = 6.1 Hz, 1H, *i*-Pr), 4.41 (d, *J* = 3.3 Hz, 1H, methine) , 3.93 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.75 (s, 6H, OMe), 3.61 (d, *J* = 3.3 Hz, 1H, methine) 3.38 (s, 3H, OMe), 1.30 (d, *J* = 6.1 Hz, 3H, *i*-Pr), 1.26 (d, *J* = 6.1 Hz, 3H, *i*-Pr).^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 204.5 (C), 155.1 (C), 153.4 (C), 150.2 (C), 149.3 (C), 149.1 (C), 147.1 (C), 143.0 (C), 137.0 (C), 135.9 (C), 134.7 (C), 131.5 (C), 119.8 (CH), 115.4 (CH), 111.9 (CH), 104.9 (CH), 100.8 (CH), 71.3 (CH), 65.0 (CH), 60.8 (CH_3), 60.7 (CH_3), 60.1 (CH_3), 56.2 (CH_3), 56.0 (CH_3), 55.9 (CH_3), 22.0 (CH_3), 21.8 (CH_3).



(±)*trans*-3-(3'-Isopropoxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3'',4'',5''-trimethoxyphenyl)-1-indenone

(±)*trans*-3-(3'-Isopropoxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3'',4'',5''-trimethoxyphenyl)-1-indanone (0.0801 g, 0.145 mmol) and DDQ (50 mg, 0.22 mmol) were dissolved in dry 1,2-dichloroethane (5 mL) and stirred at 80 °C for 12h. After this time the reaction mixture was evaporated onto silica gel (0.5 g) and flash chromatographed (7:7:1 hexanes / dichloromethane / diethyl ether) to return a red solid (42.6 mg, 53.4%).: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H, Ar), 7.02 (dd, J = 8.4, 1.9 Hz, 1H, Ar), 6.91 (d, J = 1.9 Hz, 1H, Ar), 6.87 (d, J = 8.4 Hz, 1H, Ar), 6.44 (s, 2H, Ar), 4.37 (m, J = 6.1 Hz, 1H, *i*-Pr), 3.91 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.62 (s, 6H, OMe), 3.33 (s, 3H, OMe), 1.24 (d, J = 6.1 Hz, 3H, *i*-Pr). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 195.6 (C), 152.7 (C), 154.3 (C), 152.7 (C), 150.8 (C), 147.7 (C), 146.6 (C), 137.3 (C), 131.4 (C), 130.2 (C), 128.6 (C), 126.9 (C), 126.7 (C), 126.6 (C), 122.0 (CH), 116.5 (CH), 111.2 (CH), 107.2 (CH), 104.8 (CH), 71.4 (CH), 61.5 (CH_3), 61.2 (CH_3), 60.8 (CH_3), 56.6 (CH_3), 56.0 (CH_3), 55.8 (CH_3), 21.8 (CH_3).

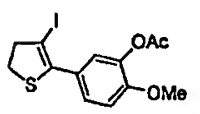
THIOPHENES AND BENZOTHIOPHENES



4-[3'-acetoxy-4'-methoxyphenyl]-3-butynyl sulfide

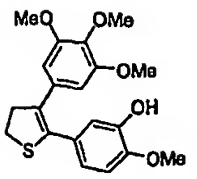
CuI (22 mg, 0.12 mmol) was added to a solution of benzyl 3-butynyl sulfide (502 mg, 2.85 mmol), 3-acetoxy-4-methoxy-iodobenzene (643 mg, 2.20 mmol) and $Pd(PPh_3)_2Cl_2$ (40 mg, 0.06 mmol) in a solution of DMF (3 mL) and Et_3N (1 mL). The resultant solution was stirred for 16 h at 18 °C. The resultant solution was diluted diethyl ether (30 mL) and washed with HClaq (1% in H_20, 30 mL) and water (3 x 30 mL), dried over $MgSO_4$ and

concentrated on to silica gel (2 g) under reduced pressure. The solid residue was subject to flash chromatography (silica gel, hexane / diethyl ether 9:1) giving the product as a viscous oil (734 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 5H), 7.28 (dd, J = 2.1, 8.4 Hz, 1H), 6.27 (d, J = 2.1 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 3.83 (s, 2H), 3.82 (s, 3H), 2.68 (s, 4H), 2.32 (s, 3H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 168.4 (C), 150.9 (C), 139.2 (C), 138.0 (C), 130.2 (CH), 128.7 (CH), 128.3 (CH), 126.8 (CH), 125.8 (CH), 115.8 (C), 112.0 (CH), 87.2 (C), 80.4 (C), 55.7 (CH_3), 36.1 (CH_2), 30.1 (CH_2), 20.5 (CH_2), 20.3 (CH_3). IR (NaCl film, cm^{-1}) 3026, 2922, 2839, 1766, 1509, 1368, 1296, 1268, 1202, 1125. MS (70 eV) *m/z* (%): 340 (M^+, 22), 298 (M^+ – CH_2CO, 65), 161 (40), 91 (100). HRMS calcd for $C_{20}H_{20}O_3S$ 340.1133. Found 340.1129.



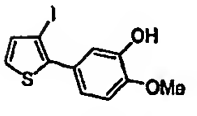
2-(3'-acetoxy-4'-methoxyphenyl)-4,5-dihydro-3-iodothiophene:

Iodine (224 mg, 0.88 mmol) was added to a solution of benzyl 4-(3'-acetoxy-4'-methoxyphenyl)-3-butynyl sulfide (300 mg, 0.88 mmol) in CH_2Cl_2 (3 mL) and the reaction mixture stirred at 18 °C for 0.15 h. After this time the solution was diluted with diethyl ether (15 mL) and was washed with $Na_2S_2O_5$ (5% w/v, 15 mL) and water (15 mL), dried over $MgSO_4$ and concentrated onto silica gel (1 g). The solid residue loaded onto a short column of silica gel (5 cm x 1.5 cm) and eluted sequently with hexane / diethyl ether 9:1 and 8:2 giving the product as a white solid (328 mg, 99%) mp = 81-3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J = 2.1, 8.4 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 3.84 (s, 3H), 3.40 – 3.20 (m_c, 4H), 2.32 (s, 3H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 168.6 (C), 151.1 (C), 138.9 (C), 138.9 (C), 127.4 (CH), 127.1 (C), 123.3 (CH), 111.6 (CH), 73.6 (C), 55.8 (CH_3), 49.4 (CH_2), 32.0 (CH_2) 20.5 (CH_3). IR (KBr disc, cm^{-1}) 2924, 2832, 1760, 1603, 1507, 1366, 1270, 1208. MS (70 eV) *m/z* (%): 376 (M^+, 72), 334 (M^+ – CH_2CO, 100), 161 (41). HRMS calcd for $C_{13}H_{13}O_3SI$ 375.9630. Found 375.9633.



2-(3'-acetoxy-4'-methoxyphenyl)-4,5-dihydro-3-(3",4",5",-trimethoxyphenyl)thiophene (GPF-60-1):

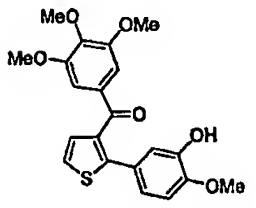
t-Butyllithium (0.36 mL, 1.7 M in hexanes, 0.61 mmol) was added to a solution 3,4,5-trimethoxyiodobenzene (88 mg, 0.30 mmol) in THF (3 mL) at –78 °C (dry-ice / acetone). Zinc chloride (42 mg, 0.31 mmol) was added and the reaction mixture warmed to room temperature. $Pd(PPh_3)_2Cl_2$, (7.0 mg, 0.01 mmol) and 2-(3'-acetoxy-4'-methoxyphenyl)-4,5-dihydro-3-iodothiophene (77 mg, 0.20 mmol) were added and the resultant solution stirred at room temperature for 6 h. Methanol (2 mL) and K_2CO_3 (140 mg, 1.01 mmol) were added to the reaction mixture and stirring continued for a further 1 h. The reaction mixture was diluted with NH_4Cl(aq) (sat., 40 mL) and extracted with diethyl ether (50 mL), dreid over $MgSO_4$ and concentratede onto silica gel (1 g). The solid residue was subjected to flash chromatography (silica gel, hexane / diethyl ether 2:1, 1:1) giving the product as white solid (63 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J = 2.1 Hz, 1H), 6.80 (dd, J = 2.1, 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.34 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.64 (s, 6H), 3.34 (m_c, 4H), 2.32 (s, 3H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 168.6 (C), 151.1 (C), 138.9 (C), 138.9 (C), 127.4 (CH), 127.1 (C), 123.3 (CH), 111.6 (CH), 73.6 (C), 55.8 (CH_3), 49.4 (CH_2), 32.0 (CH_2) 20.5 (CH_3). IR (KBr disc, cm^{-1}) 2924, 2832, 1760, 1603, 1507, 1366, 1270, 1208. MS (70 eV) *m/z* (%): 376 (M^+, 72), 334 (M^+ – CH_2CO, 100), 161 (41). HRMS calcd for $C_{13}H_{14}O_3SI$ 375.9630. Found 375.9633.



2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (272 mg, 1.2 mmol) was added to a solution of 2-(3'-acetoxy-4'-methoxyphenyl)-4,5-dihydro-3-iodothiophene (376 mg, 1.0 mmol) in dichloromethane (4 mL). After stirring at 18 °C for 1 h the reaction mixture was concentrated onto silica gel (2 g) and the solid residue subjected to flash chromatograph (silica gel, hexane / diethyl ether 1:1) the product was obtained as a viscous resin (363 mg,

95%). This material was not fully characterized: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.26 (d, *J* = 5.1 Hz, 1H), 7.12 (d, *J* = 5.1 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 2.34 (s, 3H).

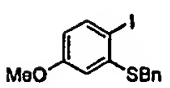
The resin was dissolved in methanol (6 mL) and K_2CO_3 (690 mg, 5.0 mmol) added and the resultant slurry stirred at 18 °C for 1 h. The rection mixture was then diluted with NH_4Cl(aq) (sat. 50 mL) and extrated with diethyl ether (2 x 50 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated onto silica gel (2 g). The solid residue was subject to flash chromatography (silica gel, hexane / diethyl ether 2:1, 1:1) and the product obtained as a viscous oil (302 mg, 91% from 2-(3'-acetoxy-4'-methoxyphenyl)-4,5-dihydro-3-iodothiophene). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 5.4 Hz, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 7.15-7.10 (m, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.77 (br s, 1H), 3.94 (s, 3H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 146.7 (C), 145.3 (C), 142.1 (C), 136.3 (CH), 127.4 (C), 126.2 (CH), 121.4 (CH), 115.6 (CH), 110.3 (CH), 77.7 (C), 55.9 (CH_3). IR (KBr disc, cm^{-1}) 3512, 2962, 2936, 2838, 1582, 1527, 1491, 1439, 1270, 1243, 1212, 1172, 1135, 1123. MS (70 eV) *m/z* (%): 332 ($M^{+\cdot}$, 100), 317 ($M^{+\cdot} - CH_3$, 58), 289 (34). HRMS calcd for $C_{11}H_9O_2SI$ 331.9368. Found 331.9369.



2-(3'-Acetoxy-4'-methoxyphenyl)-3-(3",4",5",-trimethoxybenzoyl)thiophene (BLF-89-3):

t-Butyllithium (0.738 mL, 1.7 M in hexanes, 1.25 mmol) was added to a solution 3-iodo-2-(3'-acetoxy-4'-methoxyphenyl)thiophene (139 mg, 0.418 mmol) in dry THF (4 mL) at –78 °C (dry-ice / acetone bath). To this was added a solution of 3,4,5-trimethoxybenzoyl chloride (108 mg, 0.47 mmol) in dry THF (1.5 mL) and the reaction mixture warmed to room temperature. The mixture was diluted with diethyl ether (50 mL) and washed with $NH_4Cl_{(aq)}$ (sat., 50 mL), $NaHCO_{3(aq)}$ (5%, 60 mL) dried over $MgSO_4$ and concentrated onto silica gel (2 g). The residue was subject to flash chromatography (silca gel, hexane / diethyl ether 4:1, 2:1, 1:1) and the product obtained as a white solid (109 mg, 65%) mp =

151-2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 5.0 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.22 (dd, J = 2.1, 8.4 Hz, 1H), 7.15 (s, 2H), 6.89 (d, J = 8.4 Hz, 1H), 5.79 (br s, 1H), 3.94 (s, 6H), 3.92 (s, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 187.0 (C), 153.3 (C), 153.0 (C), 147.6 (C), 146.0 (C), 141.6 (C), 141.2 (C), 135.8 (CH), 133.4 (C), 126.8 (C), 123.1 (CH), 118.6 (CH), 112.5 (CH), 111.0 (CH), 106.7 (CH), 61.1 (CH_3), (56.4(CH_3), 56.1 (CH_3). IR (KBr disc, cm^{-1}) 3212, 2993, 2939, 2839, 1574, 1453, 1428, 1348, 1259, 1240, 1126. MS (70 eV) *m/z* (%): 400 (M^+, 100), 385 ($M^+ - CH_3$, 12). HRMS calcd for $C_{21}H_{20}O_6S$ 400.0981. Found 400.0982.

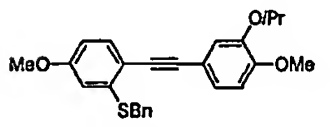


Benzyl 2-iodo-5-methoxyphenyl sulfide:

HBF_4 (50% w/v in H_2O, 14 mL) was added to a stirred suspension of 2-iodo-5-methoxyaniline[14] (5.00 g, 21.5 mmol) in H_2O (30 ml) and the suspension stirred at room temperature for 0.5 h. The resultant clear solution was cooled in an ice bath, giving a white suspension. To this suspension $NaNO_2$ (1.55 g, 22.5 mmol) in H_2O (10 mL) was added dropwise over 0.1 h and the reaction mixture warmed to room temperature. The resulting suspension was filtered, rinsed with water (50 mL) and diethyl ether (25 mL) and dried under vacuum to give the corresponding diazonium tetrafluoroborate as a cream-colored solid 7.00 g (94 %).

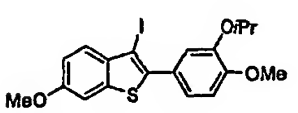
The diazonium salt (7.00 g, 20.1 mmol) obtained above was added portionwise to a solution of potassium ethyl xanthate (3.42 g, 21.0 mmol) in acetone (50 mL) at 0 °C (ice bath) over 0.15 h. The reaction mixture was stirred at 0 °C for 0.75 h and at room temperature for 1.0 h. This mixture was concentrated under reduced pressure diluted with diethyl ether (50 mL) and washed sequentially with H_2O (50 mL), KOH (2 % w/v in H_2O, 50 mL), brine (50 mL). The organic layer was died over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in methanol (50 mL) and powdered KOH (3.38 g, 60 mmol) added and the reaction mixture stirred vigorously for 3 h. The methanol was then evaporated under reduced pressure. The residue was suspended in H_2O (40 mL)

and CH_2Cl_2 (40 mL). Benzyl chloride (2.43 mL, 34.0 mmol) and *n*-Bu_4NHSO_4 (100 mg) were added and the biphasic mix stirred vigorously for 1 h. The CH_2Cl_2 layer separated and the aqueous layer extracted with CH_2Cl_2 (50 mL). The combined CH_2Cl_2 fractions dried over $MgSO_4$ and concentrated on to silica gel (8 g). The solid residue was subjected to flash chromatography (silica gel, hexane / diethyl ether 98:2) and the product was obtained as a colorless oil which crystallized upon standing at 4 °C to afford a cream solid (4.22 g, 59 %), (55 % from 2-iodo-5-methoxyaniline) mp 72-4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.7 Hz, 1H), 7.29-7.46 (m, 5H), 6.82 (d, *J* = 3.0 Hz, 1H), 6.48 (dd, *J* = 3.0, 8.7 Hz, 1H), 4.16 (s, 2H), 3.70 (s, 3 H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 159.7 (C), 142.1 (C), 139.4 (CH), 135.5 (C), 128.7 (CH), 128.3 (CH), 127.1 (CH), 113.7 (CH), 112.6 (CH), 87.4 (C), 55.0 (CH_3), 38.5 (CH_2). IR (KBr disc, cm^{-1}) 2955, 2930, 1558, 1494, 1426, 1283, 1228, 1038. MS (70 eV) *m/z* (%): 356 (M^+, 45), 229 (10), 196 (22), 181 (6), 138 (15), 123 (20), 91 (100). HRMS calcd for $C_{14}H_{13}OSI$ 355.9732. Found 355.9728



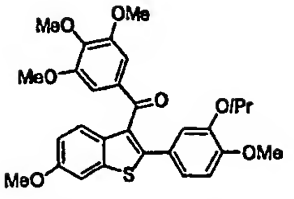
Benzyl 2-[2'-(3"-isopropoxy-4"-methoxyphenyl)-ethynyl]-5-methoxyphenyl sulfide: *n*-Butyllithium (2.5 mL, 2.5 M in hexanes, 6.25 mmol) was added dropwise to a solution of *β,β*-dibromo-3-isopropoxy-4-methoxystyrene[13] (1.09 g, 3.12 mmol) in THF (10 mL) at -78 °C (dry-ice / acetone). After the addition was complete the cold bath was removed and the reaction mixture allowed to warm to room temperature over 0.33 h. Dry zinc chloride (426 mg, 3.12 mmol) was then added and after it dissolved (approximately 3 min), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.05 mmol) and 2-iodo-5-methoxyphenyl sulfide (890 mg, 2.50 mmol) were added. The resultant solution was stirred at room temperature for 1 h then diluted with diethyl ether (30 mL) washed with $NH_4Cl_{(aq)}$ (saturated solution in H_2O, 30 mL) and brine (30 mL) dried over $MgSO_4$, and concentrated onto silica gel (3g). The solid residue was subjected to flash chromatography (silica gel, hexane / diethyl ether 9:1 then 3:1) to give the product (*Rf* = 0.25, 3:1) as a white solid (1.00 g, 96 %) mp = 67-8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 1H), 7.40-7.24 (m, 5H), 7.15 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.09 (d, *J* = 1.8 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H),

6.68 (dd, J = 2.4, 8.4 Hz, 1H), 4.55 (septet, J = 6.0 Hz, 1H), 4.23 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 159.5 (C), 150.8 (C), 146.9 (C), 141.1 (C), 136.8 (C), 133.6 (CH), 129.0 (CH), 128.6 (CH), 127.3 (CH), 125.1 (CH), 118.4 (CH), 115.6 (C), 115.4 (C), 113.3 (CH), 111.7 (CH), 111.2 (CH), 94.3 (C), 85.6 (C), 71.5 (CH), 56.0 (CH_3), 55.4 (CH_3), 37.5 (CH_2), 22.1 (CH_3). IR (KBr disc, cm^{-1}) 2973, 2835, 1594, 1509, 1471, 1410, 1324, 1288, 1263, 1246, 1136, 1116, 1053. MS (70 eV) *m/z* (%): 418 (M^+, 100), 376 (M^+ - CH_2=$CHCH_3$, 34), 341 (43), 299 (69), 253 (58) 91 (80). HRMS calcd for $C_{26}H_{26}O_3S$ 418.1603. Found 418.1601.



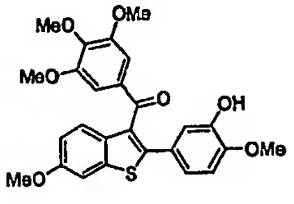
2-(3'-Isopropoxy-4'-methoxyphenyl)-3-iodo-6-methoxybenzo[*b*]thiophene:

Iodine (556 mg, 2.19 mmol) was added to a solution of benzyl 2-[2'-(3"-isopropoxy-4"-methoxyphenyl)-ethynyl]-5-methoxyphenyl sulfide (900 mg, 2.15 mmol) in CH_2Cl_2 (25 mL) and the solution stirred at room temperature for 1 h. After this time the solution was washed with $Na_2S_2O_5$ (5% w/v, 30 mL), dried over $MgSO_4$ and concentrated onto silica gel (5 g). The solid residue loaded onto a short column of (5 cm x 2 cm) and eluted with hexane and hexane / diethyl ether 3:1 to give the product (R_f = 0.33, 3:1)) as a white solid (950 mg, 97 %), mp = 102-3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 2.1 Hz, 8.4 Hz, 1H), 7.07 (dd, J = 2.4, 8.7 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 4.63 (septet, J = 6.3 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 1.45 (d, J = 6.3 Hz, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 158.0 (C), 150.5 (C), 146.7 (C), 139.5 (C), 139.3 (C), 135.9
(C), 126.9 (C), 126.5 (CH), 122.6 (CH), 116.7 (CH), 115.1 (CH), 111.4 (CH), 104.3 (CH), 77.7 (C), 71.3 (CH), 55.9 (CH_3), 55.6 (CH_3), 22.1 (CH_3). IR (KBr disc, cm^{-1}) 2974, 2920, 2835, 1600, 1530, 1493, 1471, 1261, 1224, 1138, 1020. MS (70 eV) *m/z* (%): 454 (M^+, 66), 412 (M^+ - CH_2=$CHCH_3$, 58), 397 (26), 279 (24), 149 (100). Calcd for $C_{19}H_{19}O_3SI$ C: 50.23; H: 4.22. Found C: 50.27; H: 4.19.



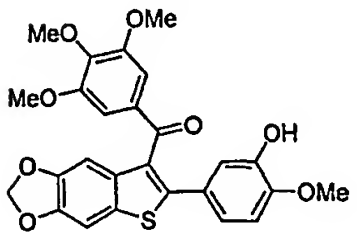
2-(3'-Isopropoxy-4'-methoxyphenyl)-6-methoxy-3-(3",4",5"-trimethoxybenzoyl)benzo[*b*]thiophene:

t-Butyllithium (0.52 mL, 1.7 M in hexanes, 0.88 mmol) was added to a solution 3-iodo-2-(3'-isopropoxy-4'-methoxyphenyl)-6-methoxybenzo[*b*]thiophene (200 mg, 0.44 mmol) in dry THF (4 mL) at –78 °C (dry-ice / acetone bath). To this was added a solution of 3,4,5-trimethoxybenzoyl chloride (108 mg, 0.47 mmol) in dry THF (1.5 mL) and the reaction mixture warmed to room temperature. The mixture was diluted with diethyl ether (50 mL) and washed with $NH_4Cl_{(aq)}$ (sat., 50 mL), $NaHCO_{3(aq)}$ (5%, 60 mL) dried over $MgSO_4$ and concentrated onto silica gel (2 g). The residue was subject to flash chromatography (silca gel, hexane / diethyl ether 4:1, 2:1, 1:1) and the product obtained as a colorless resin (200 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 9.0 Hz, 1H), 7.32 (d, J = 2.1 Hz, 1H), 7.10 (s, 2H), 7.00 (m, 2H), 6.85 (d, J = 2.1 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 4.30 (septet, J = 6.0 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.72 (s, 6H), 1.23 (d, J = 6.0 Hz, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 192.9 (C), 157.7 (C), 152.7 (C), 150.8 (C), 147.0 (C), 143.4 (C), 142.6 (C), 140.0 (C), 133.8 (C), 132.1 (C), 129.7 (C), 126.1 (C), 124.0 (CH), 121.8 (CH), 116.6 (CH), 114.9 (CH), 111.6 (CH), 107.3 (CH), 104.3 (CH), 71.5 (CH), 60.8 (CH_3), 56.0 (CH_3), 55.8 (CH_3), 55.5 (CH_3), 21.8 (CH_3). IR (NaCl film, cm^{-1}) 2936, 1644, 1581, 1531, 1501, 1473, 1413, 1228, 1126. MS (70 eV) *m/z* (%): 522 (M^+, 100), 480 (M^+ - CH_2=$CHCH_3$, 58), 301 (7), 195 (18). HRMS calcd for $C_{29}H_{30}O_7S$ 522.1712. Found 522.1716



2-(3'-Hydroxy-4'-methoxyphenyl)-6-methoxy-3-(3",4",5"-trimethoxybenzoyl)benzo[*b*]thiophene (BLF-86-1):

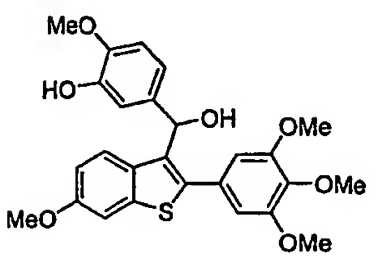
Aluminium trichloride (86 mg, 0.64 mmol) was added to a solution of 2-(3'-Isopropoxy-4'-methoxyphenyl)-6-methoxy-3-(3",4",5"-trimethoxybenzoyl)benzo[*b*]thiophene (140 mg, 0.27 mmol) in dry dichloromethane (4 mL) and the solution stirred at room temperature for 1.5 h. After this time $NH_4Cl_{(aq)}$ (sat., 20 mL) was added and the mixture extracted with diethyl ether (20 mL) dried over $MgSO_4$ and concentrated onto silica gel (1 g). The residue was subject to flash chromatography (silica gel, hexane / dichloromethane / diethyl ether 3:3:1) giving the product as a white solid (112 mg, 87%), mp = 123-5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.06 (s, 2H), 7.00 (dd, J = 2.4, 9.0 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.83 (dd, J = 2.1, 9.0 Hz, 1H), 6.64 (d, J = 9.0 Hz, 1H), 5.68 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.73 (s, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 192.9 (C), 157.7 (C), 152.6 (C), 146.9 (C), 146.4 (C), 143.7 (C), 142.3 (C), 140.0 (C), 133.7 (C), 132.4 (C), 129.9 (C), 126.7 (C), 124.2 (CH), 121.3 (CH), 115.1 (CH), 114.9 (CH), 110.4 (CH), 107.3 (CH), 60.8 (CH_3), 56.0 (CH_3), 55.8 (CH_3), 55.5 (CH_3). IR (KBr disc, cm^{-1}) 3402, 2934, 1649, 1580, 1499, 1474, 1413, 1324, 1266, 1228, 1158, 1125. MS (70 eV) *m/z* (%): 480 (M^+, 100), 301 (6), 195 (7). HRMS calcd for $C_{26}H_{24}O_7S$ 480.1243. Found 480.1242.



2-(3'-Hydroxy-4'-methoxyphenyl)-5,6-methylendioxy-3-(3",4",5"-trimethoxybenzoyl)benzo[*b*]thiophene (BLF-53-3)

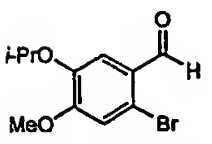
Compound **BLF-53-3** was prepared using a similar of reaction sequence as described for **BLF-86-1** giving the product as a white solid, mp = 156-7 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.21 (s, 1H), 7.05 (s, 2H), 6.95 (d, J = 2.1 Hz, 1H), 6.80 (dd, J = 2.1, 8.4 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.03 (s, 2H), 5.56 (s, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.75 (s, 6H). ^{13}C NMR + APT (75.5 MHz, $CDCl_3$) δ 192.9 (C), 152.7 (C), 147.3 (C), 147.0 (C), 146.9 (C), 145.5 (C), 144.6 (C), 142.4 (C), 134.4 (C), 132.5 (2x C), 130.1 (C),

126.9 (C), 121.3 (CH), 115.1 (CH), 110.5 (CH), 107.4 (CH), 102.5 (CH), 101.5 (CH_2), 101.1 (C), 60.9 (CH_3), 56.1 (2x CH_3), 55.9 (CH_3). IR (KBr disc, cm^{-1}) 3418, 2939, 1628, 1582, 1501, 1465, 1335, 1279, 1232, 1124. MS (70 eV) *m/z* (%): 494 (M^+, 100), 480 (3), 301 (10)267 (8). HRMS calcd for $C_{26}H_{22}O_8S$ 494.1035. Found 494.1038.



3-(α-Hydroxy-3'-hydroxy-4'-methoxybenzyl)-6-methoxy-3-(3",4",5"-trimethoxybenzoyl)benzo[*b*]thiophene (BLF-34-3):

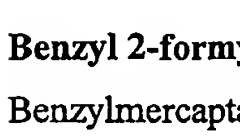
Compound **BLF-34-3** was prepared using a similar of reaction sequence as described for **BLF-86-1** except that *O*-acylisovanillin was used as the electrophile (**9**) and the product deacetylated in situ by addition of methanol and K_2CO_3, giving the product as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4 Hz, 1H), 9.29 (d, J = 2.1 Hz, 1H), 7.00 (d, J = 2.1 Hz, 1H), 6.82 (m, 2H), 6.80 (d, J = 8.4 Hz, 1H), 6.69 (s, 2H) 6.20 (br s, 1H), 5.62 (br s, 1H), 3.88 (s, 3H), 3.82 (s, 6H), 3.78 (s, 6H).



2-Bromo-5-isopropoxy-4-methoxybenzaldehyde

NBS (1.19 g, 6.70 mmol) was added to a solution of isopropyl isovanillin ether (1.24 g, 6.39 mmol), in DMF (6 mL) at room temperature, and heated to 80 °C. The reaction was monitored by TLC (eluent, hexane / diethylether 1:1, product R*f* = 0.63) and after 7 h was cooled to room temperature. The solution was diluted with diethylether (100 mL), washed with $Na_2S_2O_5$ (5% w/v, 100 mL), water (2 x 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (5 g). The solid residue was subjected to flash chromatography (silica gel, hexane / diethylether 95:5, then 9:1) to give the

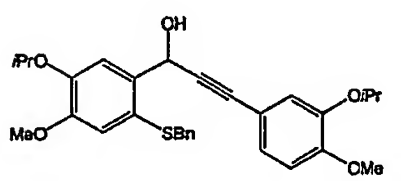
product (R*f* = 0.09, 95:5) as a white solid (1.65 g, 94%), mp = 78-79 °C. ^{1}H-NMR ($CDCl_3$) δ 10.16 (s, 1H, -CHO), 7.41 (s, 1H, Ar-H), 7.04 (s, 1H, Ar-H), 4.61 (septet, *J* = 6.0, 1H, -OC*H*$(CH_3)_2$), 3.92 (s, 3H, -OCH_3), 1.36 (d, *J* = 6.0 Hz, 6H, -OCH(C*H*$_3)_2$). ^{13}C-NMR ($CDCl_3$) δ 190.8 (C=O), 155.6, 147.1 (C-O), 126.4 (*C*-CHO), 120.0 (C-Br), 115.8, 113.5 (C-H), 71.5 (-*C*H$(CH_3)_2$), 56.4 (-OCH_3), 21.8 (2× -CH(*C*H$_3)_2$). LRMS (Calculated for $C_{11}H_{13}O_3{}^{81}Br$): m/z = 274 (21) (M^+), 232 (100) (M^+ - CH_2=CH-CH_3). HRMS Calculated for $C_{11}H_{13}O_3{}^{81}Br$ = 274.0027. Found = 274.0024. IR (KBr disc, cm^{-1}) ν max = 2971, 1681, 1587, 1508, 1432, 1386, 1268, 1217, 1158, 1109.



Benzyl 2-formyl-4-isopropoxy-5-methoxyphenyl sulfide

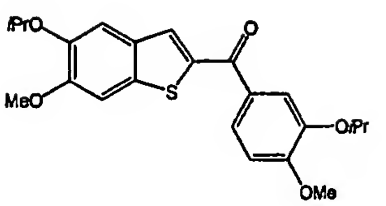
Benzylmercaptan (1.20 mL, 10.2 mmol) was added to a stirring suspension of NaH (490 mg, 10.2 mmol) in DMF at 0 °C (ice-bath). The reaction was left to stir at 0 °C until hydrogen evolution had ceased. To this was added the bromobenzaldehyde above (2.78 g, 10.2 mmol), and the reaction was left to stir for 0.25 h then warmed to room temperature. After 24 h, the reaction was diluted with diethylether (100 mL), washed with HCl (40 mL, 1 M), NaOCl (1%, 40 mL) and water (3 x 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (8 g). The solid residue was subjected to flash chromatography (silica gel, hexane / diethylether 1:4), to give the product (R*f* = 0.16) as a yellow oil (2.87 g, 89%).^{1}H-NMR ($CDCl_3$) δ 10.21 (s, 1H, 1'-H), 7.35 (s, 1H, Ar-H), 7.22 - 7.09 (m, 5H, Ar-H), 6.77 (s, 1H, Ar-H), 4.63 (septet, *J* = 5.7 Hz, 1H, -OC*H*$(CH_3)_2$), 3.98 (s, 2H, -CH_2-), 3.77 (s, 3H, -OCH_3), 1.36 (d, *J* = 5.7 Hz, -OCH(C*H*$_3)_2$). ^{13}C-NMR ($CDCl_3$) δ 190.6 (C=O), 154.5, 147.4 (C-O), 137.0, 132.2, 130.4 (C), 128.9, 128.4 (2× C-H), 127.3, 117.1, 113.1 (C-H), 71.2 (-*C*H$(CH_3)_2$), 56.1 (-OCH_3), 41.7 (CH_2), 21.8 (CH(*C*H$_3)_2$). LRMS m/z = 316 (26) (M^+), 274 (11) (M^+ - CH_2=CH-CH_3), 225 (17) (M^+ -·$CH_2(C_6H_5)$), 183 (59) (M^+ - CH_2=CH-CH_3, - ·$CH_2(C_6H_5)$) HRMS Calculated for

$C_{18}H_{20}O_3S$ = 316.1133. Found = 316.1144. IR (NaCl film, cm^{-1}) ν max = 2988, 2861, 1666, 1578, 1495, 1439, 1388, 1349, 1334, 1262, 1158.

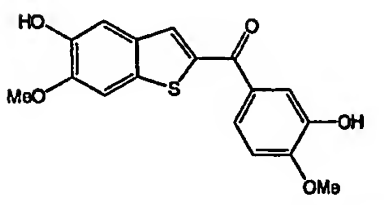


1-(2'-Benzylthio-5'-isopropoxy-4'-methoxyphenyl)-3-(3''-isopropoxy-4''-methoxyphenyl)prop-2-yn-1-ol

n-Butyllithium (0.63 mL, 1.27 mmol) was added dropwise to a solution of *β,β*-dibromo-3-isopropoxy-4-methoxystyrene[13] (221 mg, 0.633 mmol) in THF (1.5 mL) at -78 °C (dry-ice / acetone). The solution was warmed to room temperature, then recooled to -78 °C and aldehyde above (190 mg, 0.601 mmol), added and left to stir for 0.25 h. The reaction was bought to room temperature again, quenched with $NH_4Cl_{(aq)}$ (10%, 40 mL), taken up into diethylether (40 mL), washed with water (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The solid residue was subjected to flash chromatogaphy (silica gel, hexane / diethylether 3:2) to give the product (R*f* = 0.16) as a yellow resin (236.1 mg, 74%): ^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 1H, Ar-H), 7.25 - 7.09 (m, 5H, Ar-H), 7.01 (dd, *J* = 1.8, 8.3 Hz, 1H, 6"-H), 6.95 (d, *J* = 1.8 Hz, 1H, 2"-H), 6.77 (d, *J* = 8.3 Hz, 1H, 5"-H), 6.75 (s, 1H, Ar-H), 6.07 (d, *J* = 5.1 Hz, 1H, 1-OH), 4.62 (septet, *J* = 6.1 Hz, 1H, -OC*H*$(CH_3)_2$), 4.45 (septet, *J* = 6.1 Hz, 1H, -OC*H*$(CH_3)_2$), 3.99 (s, 2H, -CH_2), 3.83 (s, 3H, -OCH_3), 3.70 (s, 3H, -OCH_3), 2.40 (d, *J* = 5.1 Hz, 1H, 1-H), 1.38 (dd, *J* = 3.7, 6.1 Hz, 6H, -OCH(C*H*$_3)_2$), 1.33 (d, *J* = 6.1 Hz, 6H, -OCH(C*H*$_3)_2$). ^{13}C-NMR ($CDCl_3$) δ 150.9, 149.7, 148.0, 146.8 (C-O), 138.2, 137.5 (C), 129.1, 128.5 (2 × C-H), 127.2, 125.2 (C-H), 123.0 (C), 119.0, 118.6 (C-H) 114.8 (C), 114.2, 111.6 (C-H), 87.9, 86.4 (-C≡C-), 71.4, 71.3 (*C*H$(CH_3)_2$), 63.0 (1-C), 56.0, 55.9 (-OCH_3), 41.8 (-CH_2-), 22.2, 22.0, 21.8 (2 × CH(*C*H$_3)_2$). LRMS m/z = 506 (43) (M^+), 415 (100) (M^+ - $CH_2C_6H_5$). HRMS Calculated for $C_{30}H_{34}O_5S$ = 506.2126. Found = 506.2131. IR (NaCl film, cm^{-1}) ν max = 2978, 1592, 1504, 1386, 1264, 1110, 1044.



5-Isopropoxy-2-(3'-isopropoxy-4'-methoxybenzoyl)-6-methoxybenzo[*b*]thiophene: Iodine (418 mg, 1.65 mmol) was added to a solution of the alcohol above (835 mg, 1.65 mmol) in dichloromethane (5 mL) at room temperature. The reaction was monitored by TLC (eluent hexane / diethylether / dichloromethane 4:3:3, product R*f* = 0.53), and after 3 h the dichloromethane was removed under reduced pressure. The resultant red oil was taken up into diethylether (100 mL), and washed with $Na_2S_2O_5$ (10%, 100 mL), water (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (5 g). The solid residue was subjected to flash chromatography (silica gel, hexane / diethylether 5:3) to give the product (R*f* = 0.14) as a yellow oil (591 mg, 86%). ^{1}H-NMR ($CDCl_3$) δ 7.74 (s, 1H, Ar-H), 7.58 (dd, *J* = 2.0, 8.4 Hz, 1H, 6'-H), 7.49 (d, *J* = 2.0 Hz, 1H, 2'-H), 7.29 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 6.95 (d, *J* = 8.4 Hz, 1H, 5'-H), 4.60 (septet, *J* = 6.0 Hz, 2H, 2× -OC*H*(CH_3)$_2$), 3.96 (s, 3H, -OCH_3), 3.94 (s, 3H, -OCH_3), 1.41 (d, *J* = 2.4 Hz, 6H, -OCH(C*H*$_3$)$_2$), 1.39 (d, *J* = 2.6 Hz, 6H, -OCH(C*H*$_3$)$_2$). ^{13}C-NMR ($CDCl_3$) δ 187.7 (C=O), 153.9, 152.0, 147.0, 146.7, 141.2, 136.9, 132.6 (C), 131.3 (C-H), 130.6 (C), 123.8, 115.7, 110.5, 110.2, 103.8 (C-H), 71.6, 71.4 (*C*H(CH_3)$_2$), 56.1, 56.0 (-OCH_3), 21.9, 21.8 (2 × CH(*C*H$_3$)$_2$). LRMS m/z = 414 (59) (M^+), 330 (100), (M^+ - 2 x CH_2=CH-CH_3). HRMS Calculated for $C_{23}H_{26}O_5S$ = 414.1500. Found = 414.1493. IR (NaCl film, cm^{-1}) ν max = 2975, 1624, 1594, 1500, 1463, 1291, 1268, 1235, 1211, 1136.

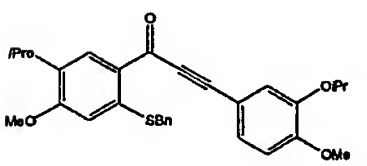


5-Hydroxy-2-(3'-hydroxy-4'-methoxybenzoyl)-6-methoxybenzo[*b*]thiophene (KH-2-2)

5-Isopropoxy-2-(3'-isopropoxy-4'-methoxybenzoyl)-6-methoxybenzo[*b*]thiophene (above) was reacted with 5 equivalents of $AlCl_3$ as described for **BLF-86-1**, giving the product, **KH-2-2**, in a 91% yield:

^{1}H-NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.47 (dd, J = 2.1, 8.3 Hz), 7.29 (s, 1H), 7.24 (s, 1H), 6.92 (d, J = 8.3 Hz), 5.78 (s, 1H), 5.75 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H).

^{13}C-NMR ($CDCl_3$) δ 187.9, 150.1, 148.5, 145.3, 144.9, 141.6, 135.2, 133.2 (C), 131.5 (C-H), 131.3 (C), 122.7, 115.5, 109.9, 109.1, 102.9 (C-H), 56.2, 55.1 (CH_3).

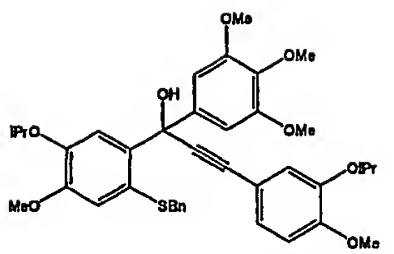


1-(2'-Benzylthio-5'-isopropoxy-4'-methoxyphenyl)-3-(3''-isopropoxy-4''-methoxyphenyl)prop-2-yn-1-one:

Prepared by DDQ oxidation of 1-(2'-benzylthio-5'-isopropoxy-4'-methoxyphenyl)-3-(3''-isopropoxy-4''-methoxyphenyl)prop-2-yn-1-ol (1.2 equivalents of DDQ in CH_2Cl_2). **OR** By reaction of benzyl (2-bromo-4-isopropoxy-5-methoxyphenyl) sulfide with one equivalent of *n*BuLi at –78 °C in THF followed by addition of 3-(3'-isopropoxy-4'-methoxyphenyl)propynoyl chloride (1.1 equivalents)

^{1}H-NMR ($CDCl_3$) δ 7.91 (s, 1H), 7.45 – 7.21 (m, 6H), 7.13 (d, J = 1.6 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.76 (s, 1H), 4.55 (septet, J = 6.1 Hz, 1H), 4.52 (septet, J = 6.1 Hz, 1H), 4.17 (s, 2H), 3.87 (s, 3H), 3.75 (s, 3H), 1.40 (d, J = 6.1 Hz, 6H), 1.37 (d, J = 6.1 Hz, 6H).

^{13}C-NMR ($CDCl_3$) δ 176.0, 154.3, 152.6, 146.9, 143.4, 136.9, 136.4 (C), 128.7, 128.5, 127.2, 126.9, (C-H), 126.7 (C), 120.9, 119.0 (C-H), 112.0 (C), 111.5, 109.2, (C-H), 93.4, 86.8 (C), 71.9, 71.4 (C-H), 55.9, 55.8 (CH_3), 37.3 (CH_2), 21.9, 21.8 (CH_3).

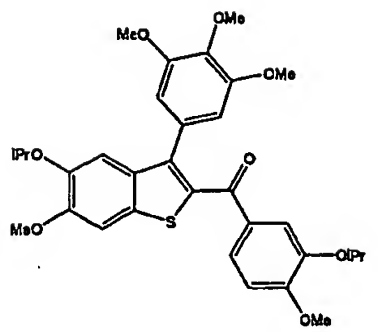


1-(2'-benzylthio-5'-isopropoxy-4'-methoxyphenyl)-1-(3'',4'',5''-trimethoxyphenyl)-3-(3'''-isopropoxy-4'''-methoxyphenyl)prop-2-yn-1-ol:

t-BuLi (0.57 mL, 0.938 mmol) was added dropwise to a solution of iodo-3,4,5-trimethoxybenzene (138 mg, 0.469 mmol) in THF (3 mL) at -78°C (dry-ice / acetone bath), and left to stir for 0.5 h. After this time, 1-(2'-benzylthio-5'-isopropoxy-4'-methoxyphenyl)-3-(3''-isopropoxy-4''-methoxyphenyl)prop-2-yn-1-one (237 mg, 0.469 mmol) was dissolved in THF (2 mL) and added dropwise to the solution. After further stirring for 0.5 h, the solution was warmed to room temperature and quenched with $NH_4Cl_{(aq)}$ (40 mL, 10%). The solution was extracted with diethyl ether (3 x 50 mL), washed with water (40 mL), dried over $MgSO_4$, and concentrated onto silica gel (2 g). The solid residue was subjected to flash chromatography (silica gel, hexanes : diethyl ether, 1:1, 2:3 sequential elution) to give the product (Rf = 0.21, 3:2 diethyl ether : hexanes) as a yellow oil (277 mg, 88%).

^{1}H-NMR ($CDCl_3$) δ 7.23 - 7.20 (m, 3H), 7.14 (s, 1H), 7.10 - 7.05 (m, 3H), 6.99 (d, J = 2 Hz, 1H), 6.90 (s, 2H), 6.78 (d, J = 8.4 Hz), 6.59 (s, 1H), 5.38 (s, 1H), 4.42 (septet, J = 6.1 Hz, 2H), 3.87 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.81 (s, 6H), 3.59 (s, 3H), 1.35 (d, J = 6.1 Hz, 6H), 1.33 (d, J = 6.1 Hz, 6H).

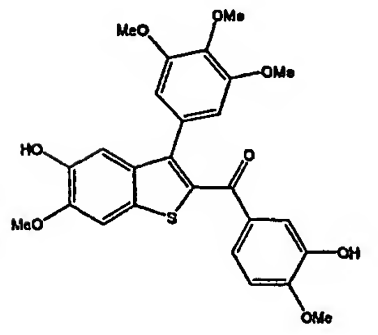
^{13}C-NMR ($CDCl_3$) 152.8, 151.1, 148.8, 146.9, 146.4, 140.6, 139.7, 137.4, 137.3 (C), 129.3, 128.4, 127.2, 125.2 (C-H), 122.5 (C), 120.7, 118.6, 115.8 (C-H), 114.6 (C), 111.6, 104.3 (C-H), 90.1, 88.0, 75.4 (C), 71.4, 71.2 (C-H), 60.8, 56.9, 55.9, 55.8 (CH_3), 41.2 (CH_2), 21.9, 21.8 (CH_3).



5-Isopropoxy-2-(3'-isopropoxy-4'-methoxybenzoyl)-6-methoxy-3-(3'',4'',5''-trimethoxyphenyl)benzo[*b*]thiophene:

Iodine (80 mg, 0.317 mmol) was added to a solution of 1-(2'-benzylthio-5'-isopropoxy-4'-methoxyphenyl)-1-(3'',4'',5''-trimethoxyphenyl)-3-(3'''-isopropoxy-4'''-methoxyphenyl)prop-2-yn-1-ol (208 mg, 0.309 mmol) in CH_2Cl_2 (3 mL) and left to stir for 0.5 h. After this time, the solution was quenched with $Na_2S_2O_{5\,(aq)}$ (40 mL, 5%), and the solution extracted with diethyl ether (3 x 50 mL), washed with water (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The solid residue was subjected to flash chromatography (silica gel, hexanes : diethyl ether, 2:3 eluent) to give the product (Rf = 0.21) as a red solid (164 mg, 91%).

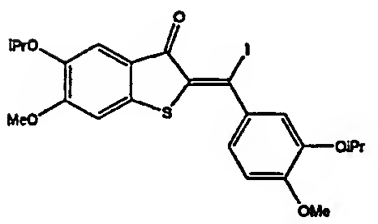
^{1}H-NMR ($CDCl_3$) δ 6.95 (dd, J = 1.9, 8.4 Hz, 1H), 6.91 (d, J = 1.9 Hz, 1H), 6.90 (s, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.73 (s, 1H), 6.56 (s, 1H), 4.53 (septet, J = 6.0 Hz, 1H), 4.38 (septet, J = 6.0 Hz, 1H), 3.89 (s, 6H), 3.85 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 1.40 (d, J = 6.0 Hz, 6H), 1.32 (d, J = 6.0 Hz, 6H)



5-Hydroxy-2-(3'-hydroxy-4'-methoxybenzoyl)-6-methoxy-3-(3'',4'',5''-trimethoxyphenyl)benzo[*b*]thiophene:

Aluminium trichloride (17 mg, 0.138 mmol) was added to a solution of 5-Isopropoxy-2-(3'-isopropoxy-4'-methoxybenzoyl)-6-methoxy-3-(3'',4'',5''-trimethoxyphenyl)benzo[*b*]thiophene (27 mg, 0.0466 mmol) in CH_2Cl_2 (3 mL) at room temperature and left to stir. After 1 h, a further amount of aluminium trichloride (17 mg, 0.138 mmol) was added. After a further 2 h, the solution was quenched with $NH_4Cl_{(aq)}$ (30 mL, 10%), extracted with ethyl acetate (3 x 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The solid residue was subjected to flash chromatography (silica gel, hexanes : diethyl ether, 4:1, 7:3, 3:2, 1:1 sequential elution) to give the product as a yellow solid (21 mg, 92%).

^{1}H-NMR ($CDCl_3$) δ 7.33 (s, 1H), 7.32 (s, 1H), 7.19 (dd, J = 2.1, 8.3 Hz, 1H), 7.1 (d, J = 2.1 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 6.47 (s, 2H), 5.78 (s, 1H), 5.42 (s, 1H), 4.04 (s, 3H), 3.84 (s, 3H), 3.75 (s, 9H).

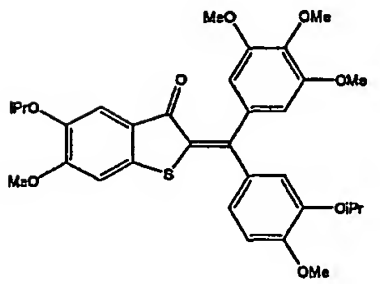


2-(α-iodo-3'-isopropoxy-4'-methoxybenzylidene)-5-isopropoxy-6-methoxybenzo[*b*]thiophen-3-one:

Iodine (370 mg, 1.47 mmol) was added to a solution of 1-(2'-benzylthioxy-5'-isopropoxy-4'-methoxyphenyl)-3-(3''-isopropoxy-4''-methoxyphenyl)prop-2-yn-1-one (740 mg, 1.47 mmol) in CH_2Cl_2 (20 mL) and stirred for 0.5 h. After this time, the solution was quenched with $Na_2S_2O_{5(aq)}$ (200 mL), extracted with diethyl ether (3 x 150 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (7 g). The solid residue was subjected to flash chromatography (silica gel, hexanes : diethyl ether, 3:2, 2:3 sequential elution), to give the product as a yellow oil (668 mg, 84%).

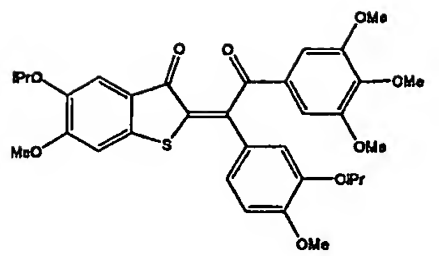
^{1}H-NMR ($CDCl_3$) δ 7.39 (s, 1H), 7.09 (dd, J = 2.1, 8.4 Hz, 1H), 7.08 (s, 1H), 7.05 (d, J = 2.1, 1H), 7.04 (dd, J = 2.0, 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz), 6.96 (d, J = 2.0 Hz, 1H), 6.83

(d, J = 8.4 Hz, 1H), 6.80 (s, 1H), 6.75 (s, 1H), 4.63 - 4.46 (m, 4H), 3.95 (s, 3H), 3.90 (s, 6H), 3.85 (s, 3H), 1.42 - 1.35 (m, 24H). ^{13}C-NMR ($CDCl_3$) δ 178.9, 165.1, 157.2, 156.9, 151.5, 146.6, 146.3, 145.9, 139.3, 138.0, 137.7, 134.2, 133.6, 126.8, 124.9 (C), 122.1, 121.8, 116.2, 115.9 (C-H), 114.0 (C), 112.2, 111.4, 110.8, 110.5, 105.3, 103.8 (C-H), 98.7 (C), 71.6 (C-H), 56.5, 56.1 (CH_3), 21.9, 21.8 (CH_3).



2-[α-(3"-isopropoxy-4"-methoxyphenyl)-3',4',5'-trimethoxybenzylidene]-5-isopropoxy-6-methoxybenzo[*b*]thiophen-3-one.

t-Butyllithium (0.35 mL, 0.55 mmol) was added dropwise to a solution of iodo-3,4,5-trimethoxybenzene (80 mg, 0.27 mmol) in THF (3 mL) at –78 °C (dry-ice / acetone bath). After 0.1 h, dry zinc chloride (36 mg, 0.27 mmol) was added and the reaction warmed to room temperature. After 0.25 h, $Pd(PPh_3)_2Cl_2$ (4 mg, 3%) was added, followed by iodoaurone (68 mg, 0.13 mmol). The reaction was left to stir for 18 h, after which the solution was diluted with diethyl ether (40 mL), washed with water (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether, 3:2, 2:3, 1:3 sequential elutions) to give the product as a white solid (52 mg, 69%). ^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 1H), 7.28 (s, 1H), 6.97 (dd, J = 2.0, 8.4 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 4.55 (septet, J = 6.1 Hz, 1H), 4.39 (septet, J = 6.1 Hz, 1H), 3.95 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.1 (s, 6H), 1.38 (d, J = 6.1 Hz, 6H), 1.24 (d, J = 6.1 Hz, 6H).



2-[2-Oxo-1-(3'-isopropoxy-4'-methoxyphenyl)-2-(3",4",5"-trimethoxyphenyl)-ethylidene]-5-isopropoxy-6-methoxybenzo[*b*]thiophen-3-one.

t-Butyllithium (0.37 mL, 0.59 mmol) was added dropwise to a solution of iodo-3,4,5-trimethoxybenzene (87 mg, 0.29 mmol) in THF (5 mL) at -78C (dry-ice / acetone bath). After 0.1 h, dry zinc chloride (40 mg, 0.29 mmol) was added and the reaction warmed to room temperature. After 0.25 h, $Pd(PPh_3)_2Cl_2$ (4 mg, 3%) was added, and the nitrogen atmosphere replaced with carbon monoxide. The solution was stirred vigourously, and after 0.2 h iodoaurone (68 mg, 0.13 mmol) was added. The reaction was left to stir for 19 h, after which time it was diluted with diethyl ether (50 mL), washed with water (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether, 1:2, 1:3, 1:4 sequential elutions) to give the product as a white solid. ^{1}H-NMR ($CDCl_3$) δ 7.40 (s, 1H), 7.19 (dd, J = 2.1, 8.3 Hz, 1H), 7.12 (d, J = 2.1 Hz, 1H), 7.03 (s, 1H), 6.88 (s, 2H), 6.61 (d, J = 8.3 Hz, 1H), 4.62 (septet, J = 6.1 Hz, 1H), 4.58 (septet, J = 6.1 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 6H), 3.79 (s, 6H), 1.38 (d, J = 6.1 Hz, 6H), 1.33 (d, J = 6.1 Hz, 6H).

Biological Activity

A number of compounds according to the invention (Figure 11) were examined for their effects on tubulin polymerization, colchicine binding and growth of Burkitt lymphoma CA46 cells according to the procedures described in Verdier-Pinard *et al., Mol. Pharmacol.,* **1998,** 53, 62 and effects compared against Combretastatin A4(A) and benzothiophene(B) (see page 2). The results are depicted in Table 1.

Tabel 1: Effects of compounds on tubulin polymerisation, colchicine binding and growth

of Burkitt lymphoma CA46 cells (see FIGURE 11)

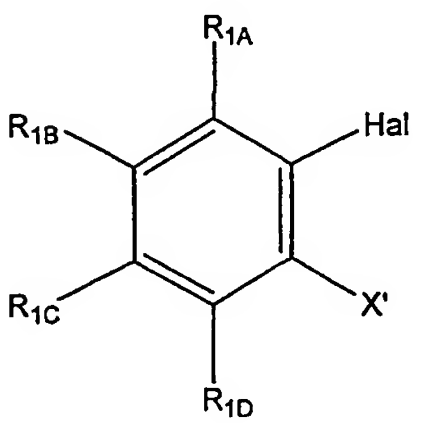
Compound	Inhibition of tubulin Polymerization[a] IC_{50} (μM)	Inhibition of colchicine binding (% inhibition)[b]		Inhibition of CA46 cell growth IC_{50} (nM)
		5 μM inhibitor inhibitor	50 μM	
(A)	2.1 ± 0.1	91	ND	1 (11[e])
(B)[c]	>40*[d]	-	28	2000 (640[e])
BLF-86-1	3.5 ± 0.3	6	61	500(520[e])
BLF-34-3	6.1 ± 0.8	5	73	>1000
BLF-53-3	>40*[d]	2	31	>1000
GPF–60-1	3.6 ± 1	64	88	390[e]
BLF-89-3	1.0 ± 0.1	67	-	300[e]
BLF-28-1	0.75	55	80	40(34[e])
BLF-68-3	>40*	-	-	>1000[e]
BLF-70-3	2.5± 0.3	17	-	400[e]
BLF-62-3	1.3± 0.2	80	-	42[e]
BLF-36-1	>40*[d]	-	-	>1000
BLF-69-3	8.8± 1.4	-	-	560[e]
BLF-61-3	4.1± 0.6	28	-	370[e]
BLF-67-3	1.6	54	-	45[e]
KH-2-2	2.4± 0.4	-	-	-
DK-12a-1	10-40	-	-	-
DK-2a-2	4-10	-	-	-

[a]The tubulin concentration was 10 μM. Inhibition of extent of assembly was the parameter measured.
[b]The tubulin concentration was 1.0 μM and the [^{3}H]colchicine concentration was 5.0 μM.
[c]Data from Pinney K.G. *et al Bloorg. Med. Chem. Let.*, 1999, 1081 and US Patent 5,886,025.
[d]The asterisk indicates that the rate but not the extent of assembly was inhibited by compound concentrations as high as 40 μM.
[e]The MCF-7 human breast carcinoma cell line was used.

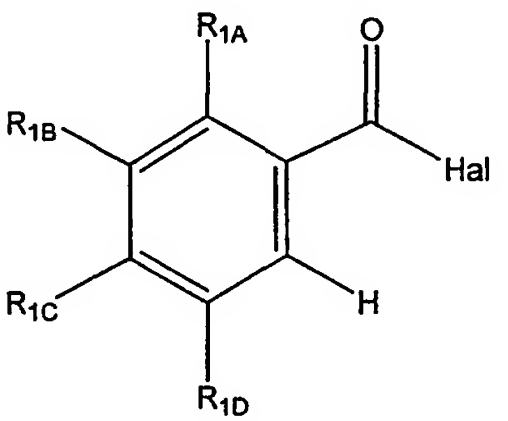
CLAIMS:

1. A combinatorial library of 2 or more chemical compounds each compound comprising the reaction product derived from at least two substrates selected from (a), (b) and (c):

(a)

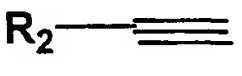
(i) 

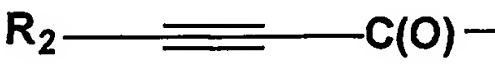
or

(ii) 

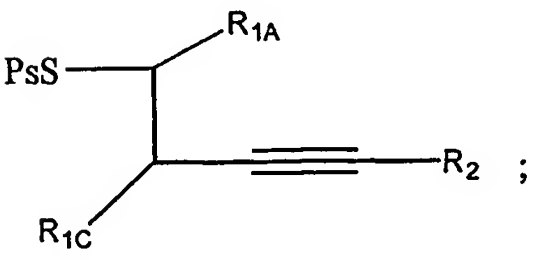
;

(b)

(i)  , or a metallated form thereof; or

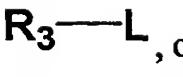
(ii)  ; or

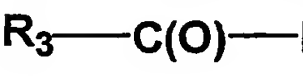
(iii)



;

(c)

(i)  , or a metallated form thereof wherein L is replaced by a metal; or

(iii)  ;

wherein

R_{1A}-R_{1D} are independently selected from hydrogen, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino or any 2 adjacent R_{1A}-R_{1D} together form

–O-CH_2-O-;

Hal is I, Br or Cl;

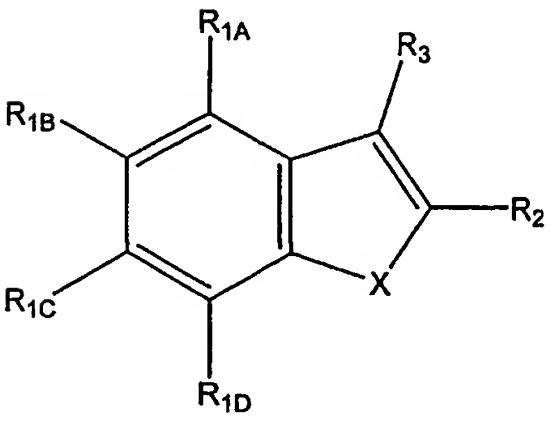
X' is OH, SPs (wherein Ps is a sulfur-protecting group capable of stabilising a positive charge), NP_N (wherein P_N is a nitrogen-protecting group); or NHR (wherein R is sulphonyl, triflouroacyl, C_{1-7}acyl, C_{1-6}alkyl or an aryl group);

L is a leaving group.

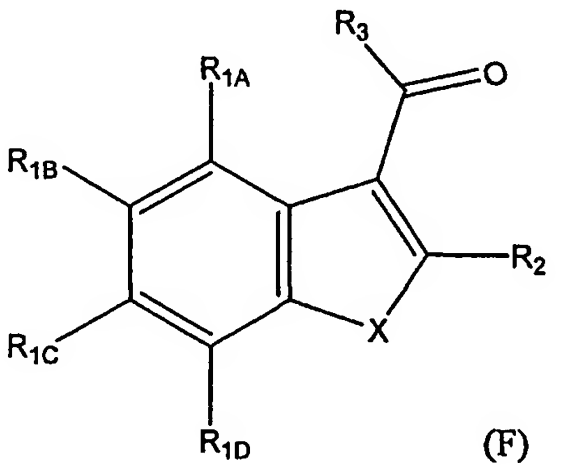
R_2 and R_3 are optionally substituted aryl groups.

2. A combinational library of compounds for screening, as potential tubulin polymerisation inhibitors, said library comprising two or more compounds of formulae (E) to (Q), said compounds being the reaction products of the following substrates:

- (a)(i), (b)(i) and (c)(i) to produce compounds of formulae (E) and (F)



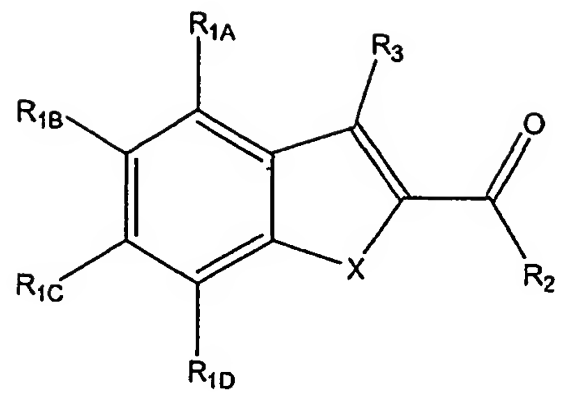
(E)



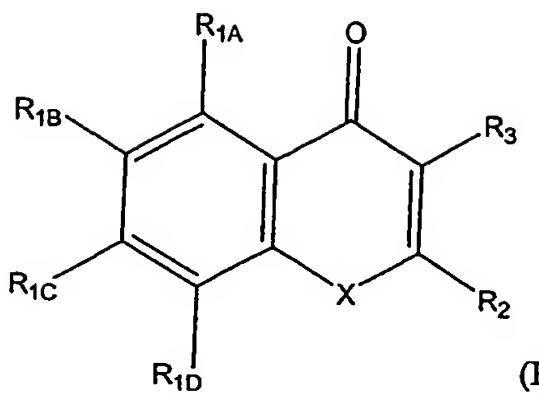
(F)

- (a)(i), (b)(i) and (c)(ii) to produce compounds of formula (F);

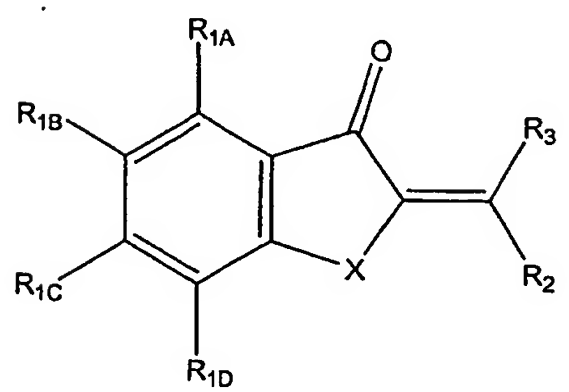
- (a)(i), (b)(ii) and (c)(i) to produce compounds of formulae (G), (H), (I), (J) or (K)



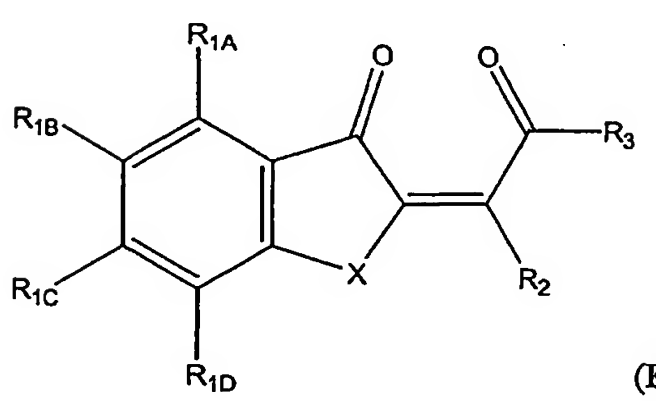
(G)



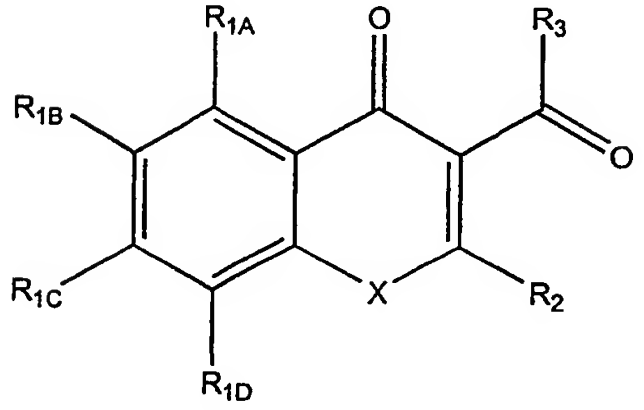
(H)



(J)

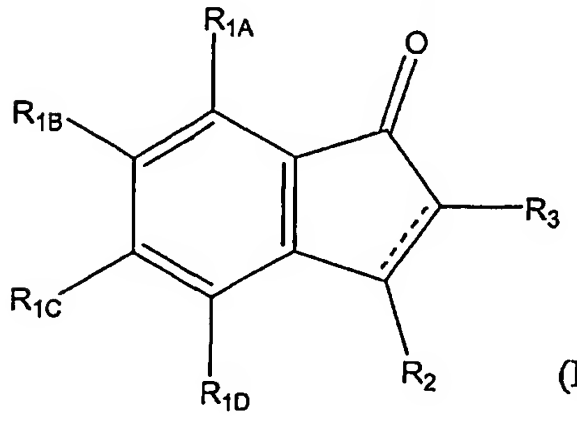


(K)



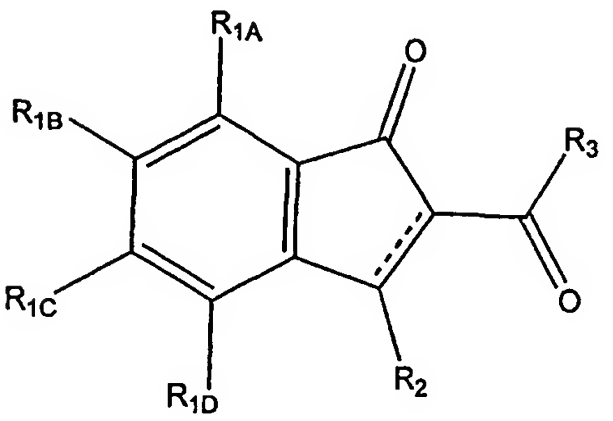
(I)

- (a)(i), (b)(ii) and (c)(ii) to produce compounds of formulae (I) and (K)
- (a)(ii), (b)(i) and (c)(i) to produce compounds of formula (L)



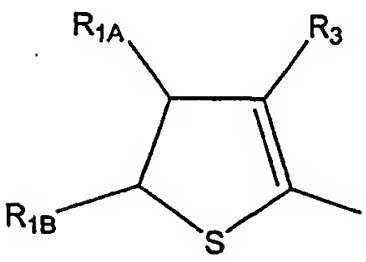
(L)

- (a)(ii), (b)(i) and (c)(ii) to produce compounds of formula (M)



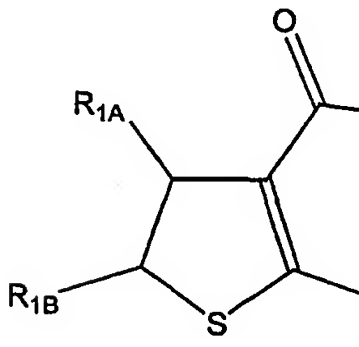
(M)

- (b)(iii) and (c)(i) to produce compounds of formula (P)



(P)

- (b)(iii) and (c)(ii) to produce compounds of formula (Q)



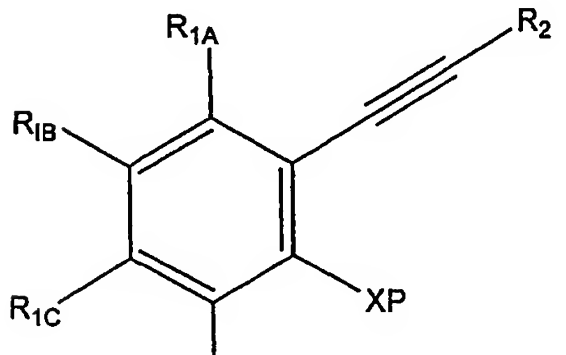
(Q)

wherein R_2, R_3, $R_{1A} - R_{1D}$, (a)(i), (a)(ii), (b)(i)-(b)(iv) and (c)(i)-(iii) are as defined in claim 1, and X=O, S, or NR (wherein R is H, sulfonyl, C_{1-6}alkyl, C_{1-7}acyl or an aryl group).

3. A combinatorial library of compounds according to claim 1 or 2, in which the compounds are further attached to a solid support surface.

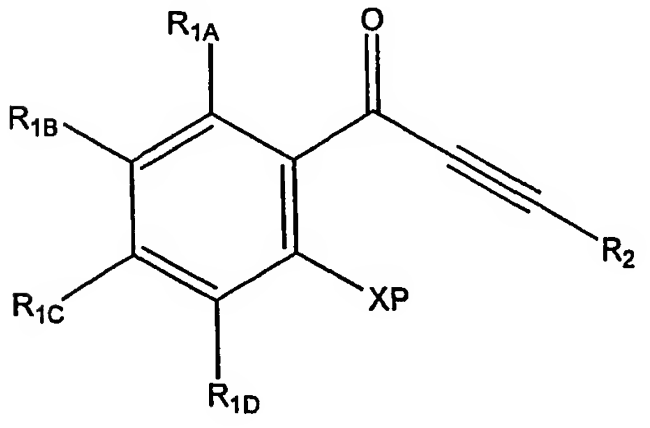
4. A combinational library of intermediates useful for the preparation of the compounds of formulae (E) – (Q) as defined in claim 2, said intermediates being the reaction products of the following substrates;

- (a)(i) and (b)(i) to produce intermediates of formula (E') for use in preparing compounds of formulae (E) and (F)

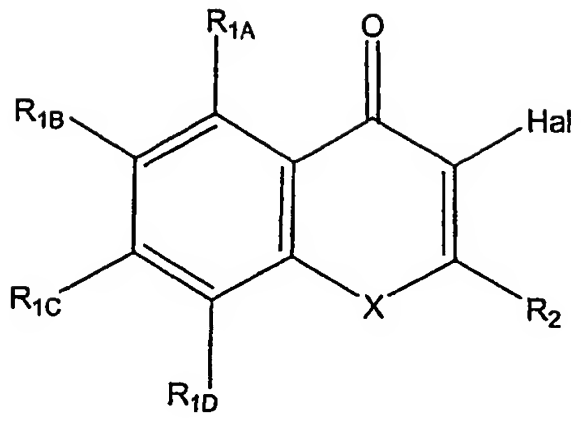


(E')

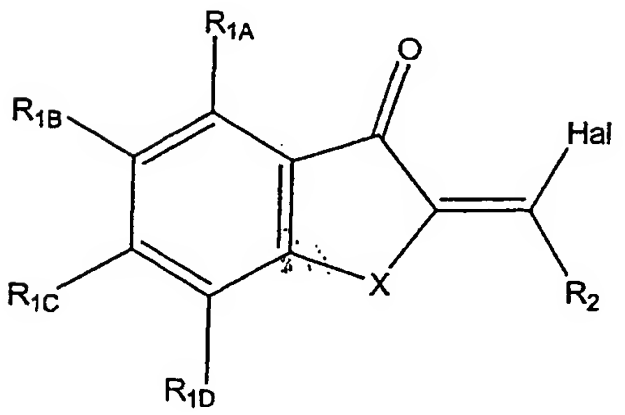
- (a)(i) and (b)(ii) to produce intermediates of formulae (F'), (G') and (H') for use in preparing compounds of formulae (G), (H), (I), (J) or (K);



(F')

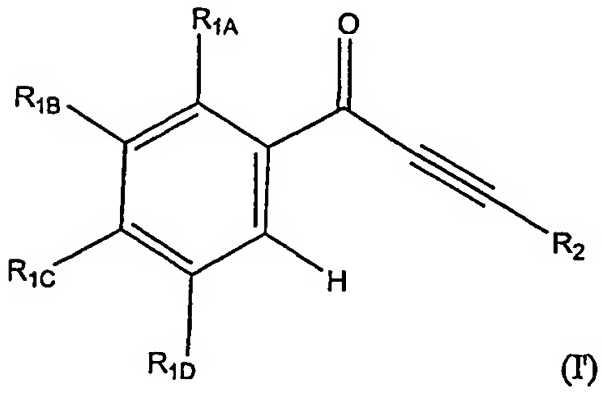


(G')

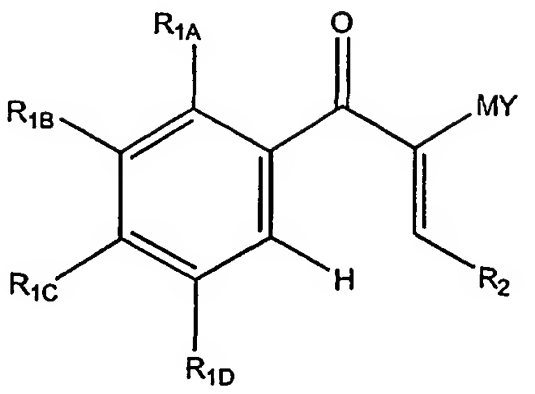


(H')

- (a)(ii) and (b)(i) to produce intermediates of formulae (I') and (J') for use in preparing compounds of formula (L) or (M)

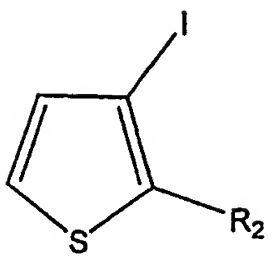


(I')



(J')

(b)(iii) with itself to produce intermediates of formulae (L')



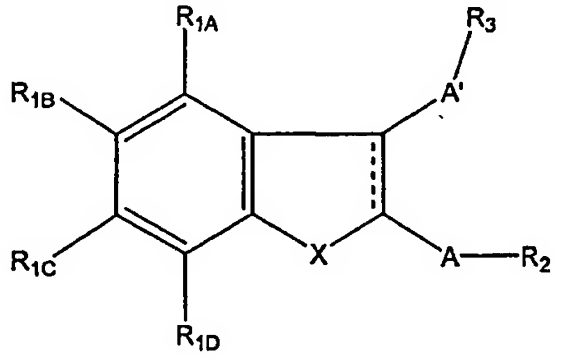
(L')

for use in preparing compounds of formulae (P) and (Q);

wherein R_{1A}-R_{1D}, R_2, R_3, X, (a)(i), (a)(ii), (b)(i)-(iv) and (c)(ii)-(iii) are as defined in claim 1, X is N, O or S, P is a protecting group and MY is $Sn(alkyl)_3$ or $B(OR)_2$, wherein R is H or alkyl.

5. A combinatorial library of intermediates according to claim 4, in which the intermediates are further attached to a solid support surface.

6. A combinatorial library of at least two compounds of formula (I):



(I)

wherein

X is selected from O, S, NR, C=O (R is H, C_{1-6}alkyl or C_{1-6}acyl);

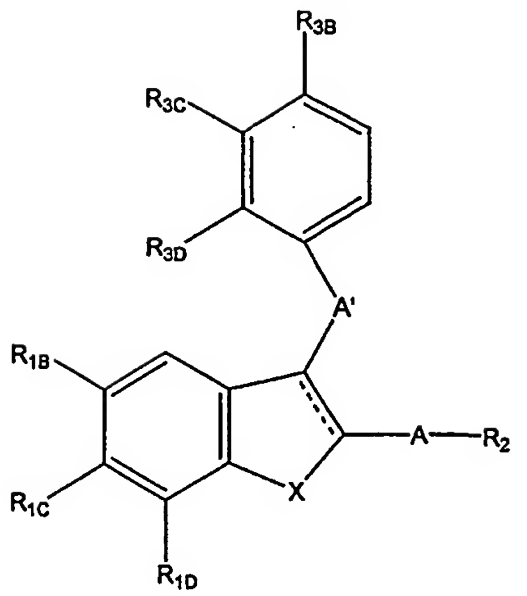
A and A' are independently selected from CH_2, C=O, CH(OR') (R' is H, C_{1-6}alkyl, C_{1-7}acyl) or a single bond;

..... is a double or single bond

R_{1A}- R_{1D} are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino, optionally substituted acylamino or any 2 adjacent R_{1A}-R_{1D} together form –O-CH_2-O-.

R_2 and R_3 are optionally substituted aryl groups.

7. A compound of formula (I'''')



(I''''')

wherein X is O, S, NR (wherein R is hydrogen, sulfonyl, C_{1-6}alkyl, C_{1-7}acyl, or an aryl group) or C=O;

R_{1B}-R_{1D} and R_{3B}-R_{3D} are independently selected from hydroxy, methoxy, and amino or any 2 adjacent R_1 and/or R_3 groups from R_{1B}-R_{1D} and R_{3B}-R_{3D} form a dioxolanyl group;

R_2 is an optionally substituted aryl group;
A and A' are independently selected from the group consisting of a single bond, C=O, CH_2, and CH(OR'), (R' is hydrogen, C_{1-6}alkyl or C_{1-7}acyl); and

provided that the compound is not;

3-(3',4',5'-trimethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(2',6'-dimethoxybenzoyl-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(3',5'-dimethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(3',4'-dimethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(4'-methoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(4'-ethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-(3',4',5'-triethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;
3-[3'-(3',4',5'-trimethoxyphenyl)propionyl]-2-(4'-methoxyphenyl)-6-

methoxybenzo[b]thiophene;

3-(3',4',5'-triethoxybenzoyl)-2-(4'-ethoxyphenyl)-6-ethoxybenzo[b]thiophene;

3-(4'-ethoxy-3',5'-dimethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;

3-(4'-N,N-dimethylaminobenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;

3-(3',4',5'-triflurobenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;

3-(2',3',4',5',6'-pentafluorobenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;

3-(3',4',5'-trimethoxybenzoyl)-2-(4'-methoxyphenyl)-benzo[b]thiophene;

3-(3',4',5'-trimethoxybenzoyl)-2-(4'-ethoxyphenyl)-6-ethoxybenzo[b]thiophene;

3-(4'-hydroxy-3',5'-dimethoxybenzoyl)-2-(4'-methoxyphenyl)-6-methoxybenzo[b]thiophene;

2-(3",4",5"-trimethoxybenzoyl)-3-(4'-methoxyphenyl)-6-methoxybenzo[b]furan;

2-(4'-methoxyphenyl)-3-(3',4',5'-trimethoxybenzoyl)-6-methoxyindole;

2-(3'-*t*-butylsiloxy-4'-methoxyphenyl)-3-(3',4',5'-trimethoxybenzoyl)-6-methoxyindole;

Disodium 2-(4'-methoxyphenyl-3'-O-phosphate)-3-(3",4",5"-trimethoxybenzoyl)-6-methoxyindole;

2-(4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;

Disodium 2-(3'-phosphormaidate-4'-methoxyphenyl)-3-(3",4",5"-trmethoxybenzoyl)-6-methoxyindole;

2-(3'-hydroxy-4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;

2-(3'-amino-4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;

Disodium 2-[(4'-methoxyphenyl)-3'-O-phosphate]-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;

2-(3'-diethylphosphoramidate-4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;

Disodium 2-(3'-phosphoramidate-4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)-4-methoxyindole;

2-(1-napth-1-yl)-3-(3",4",5"-trimethoxyphenyl)-5-methoxyindole;

2-(3',4'-methylenedioxyphenyl)-3-(3",4",5"-trimethoxyphenyl)-5-methoxyindole;

2-(furan-2-yl)-3-(3', 4', 5'-trimethoxyphenyl)-5-methoxyindole;

2-(furan-3-yl)-3-(3', 4', 5'-trimethoxyphenyl)-5-methoxyindole;

2-(5-methylfuran-2-yl)-3-(3', 4', 5'-trimethoxyphenyl)-5-methoxyindole.

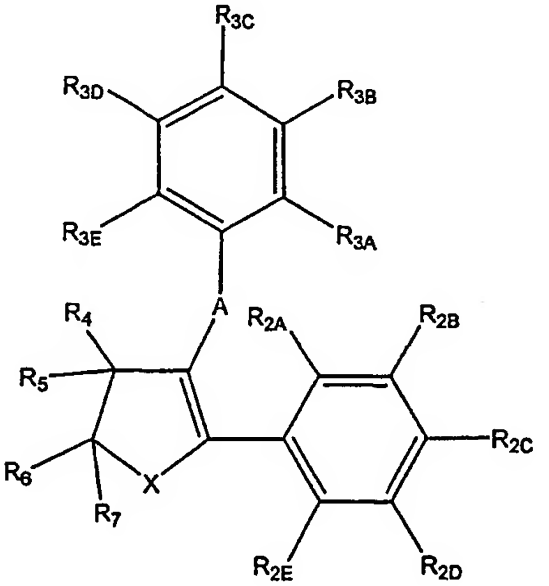
8. A compound of formula (I'''') according to claim 7 wherein X is O, C=O or NR.

9. A compound of formula (I'''') according to claim 8 wherein X is O.

10. A compound of formula (I'''') according to claim 7 wherein X is O and A' is C=O and A is a single bond.

11. A compound of formula (I'''') according to claim 7 wherein ------ represents a double bond.

12. A compound of formula (IV)



(IV)

wherein X is O, S or NR" (R" is aryl, aroyl, acyl, benzyl, alkyl or sulphonyl)

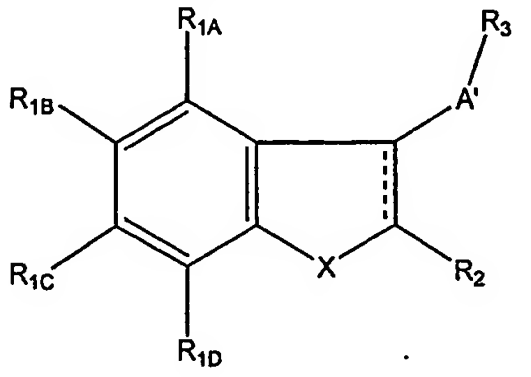
A is a single bond C=O, CH(OR') (R' is hydrogen, C_{1-6}alkyl, C_{1-7}acyl), CH_2, O, S or NR (R is hydrogen, C_{1-6} hydrogen, C_{1-6}alkyl or C_{1-7}acyl);

R_{2A}-R_{2E} and R_{3A}-R_{3E} are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino, optionally substituted acylamino or where any two adjacent R_2 and/or R_3 group from R_{2A}-R_{2D} and

R_{3A}-R_{3E} together form –O-CH_2-O-.

R_4-R_7 are independently selected from hydrogen, hydroxy, alkoxy, alkyl and amino .

13. A method of preparing a compound of formula (I')



(I')

wherein

X is O, NH or NR, (wherein R is H, sulfonyl, C_{1-6}alkyl, C_{1-7}acyl or an aryl group)

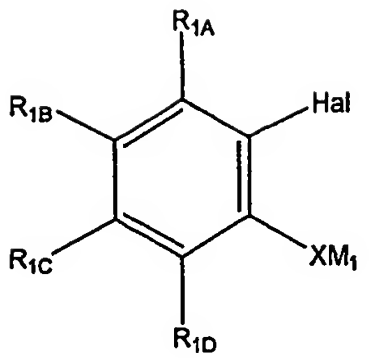
A' is independently selected from a single bond, CH_2, C=O, and CH(OR') (R' is H, C_{1-6}alkyl or C_{1-7}acyl);

R_{1A}-R_{1D} are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino, optionally substituted acylamino, or any 2 adjacent R_{1A}-R_{1D} together form –O-CH_2-O-;

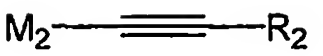
R_2 and R_3 are optionally substituted aryl groups;

said method comprising the steps of:

a) coupling a compound of formula (1) with an alkyne of formula (2) in the presence of a nickel or palladium coupling agent



(1)



(2)

wherein

R_{1A}-R_{1D}, R_2 and X are as above;

Hal is I ,Br or Cl;

M_1 is a metal or a metal species thereof, said metal selected from the group consisting of Li, Na, K, Mg, Cs and Ba;

M_2 is a metal, or a metal species thereof, said metal selected from the group consisting of Mg, Zn, Cu, B, Si, Mn, Sn, Ge and Al;

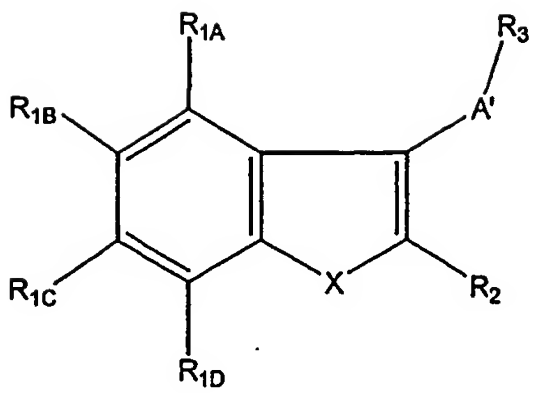
X is O, NR (R is sulfonyl, C_{1-6}alkyl or C_{1-7}acyl);

e) reacting *in situ* the resulting coupled product, with R_3-L wherein R_3 is an optionally substituted aryl group, and wherein L is a leaving group, optionally in the presence of carbon monoxide; and

f) optionally reducing the resulting product, when A' is C=O, to afford compounds in which A' = CH_2 or CH(OR').

14. A combinatorial library of compounds comprising at least two compounds of formula (I') according to claim 13.

15. A method for preparing a compound of formula (I''):



(I'')

wherein

X is S

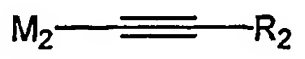
A' is selected from a single bond, CH_2, C=O, and CH(OR') (R' is H, C_{1-6}alkyl or C_{1-7}acyl);

R_{1A}-R_{1D} are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino, optionally substituted acylamino, or any two adjacent R_{1A}-R_{1D} together form -O-CH_2-O-;

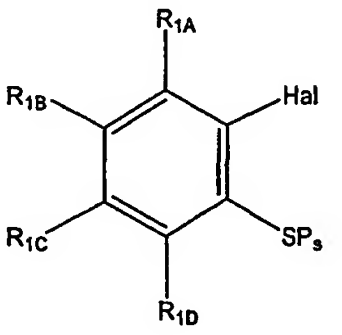
R_2 and R_3 are optionally substituted aryl groups;

said method comprising the steps of:

a) coupling a compound of formula (3) with a compound of formula (4) in the presence of a nickel or palladium coupling agent



(3)

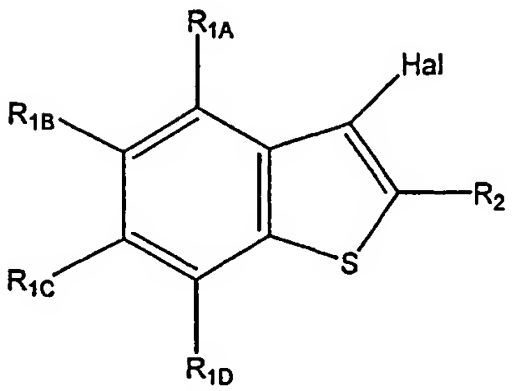


(4)

wherein

R_{1A}-R_{1D}, Hal, M_2 and R_2 are as above, and P_s is a sulfur protecting group capable of stabilizing a positive charge;

b) cyclising the resulting coupled product in the presence of a Hal^+ producing reagent to give (5)



(5)

wherein

Hal is Cl, Br or I;

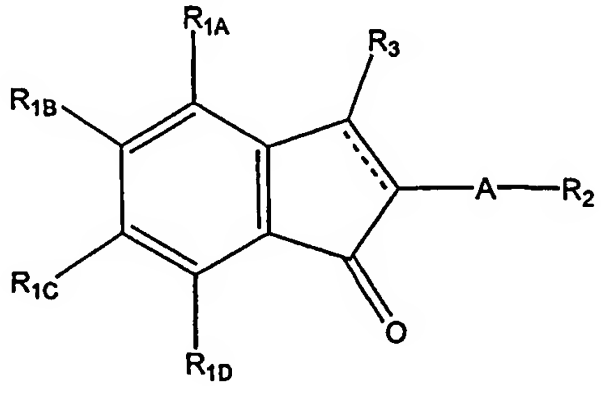
c) coupling (5) with either the moiety $R_3C(O)$- or R_3-

wherein R_3 is an optionally substituted aryl group; and

g) optionally reducing the coupled product, when A' is C=O, to afford compounds in which A' = CH_2 or CH(OR').

16. A combinatorial library of compounds comprising at least two compounds of formula (I") according to claim 15.

17. A method for preparing a compound of formula (I'")



(I'")

wherein

A is selected from a single bond, CH_2, C=O and CH(OR') (R' is H, C_{1-6}alkyl or C_{1-7}acyl);

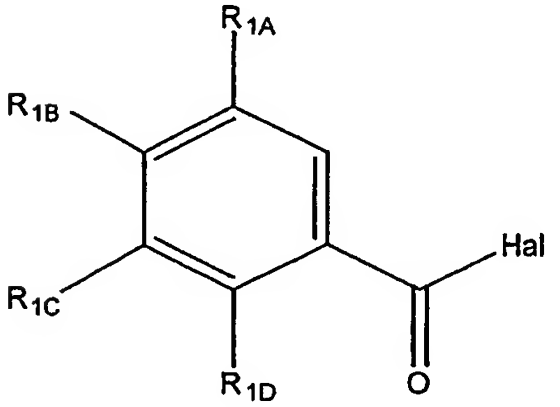
R_{1A}-R_{1D} are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino or any 2 adjacent R_{1A}-R_{1D} together form $-O-CH_2-O$;

..... is an optional double bond;

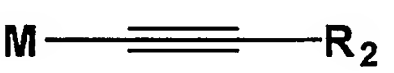
R_2 and R_3 are optionally substituted aryl groups;

said method comprising the steps of:

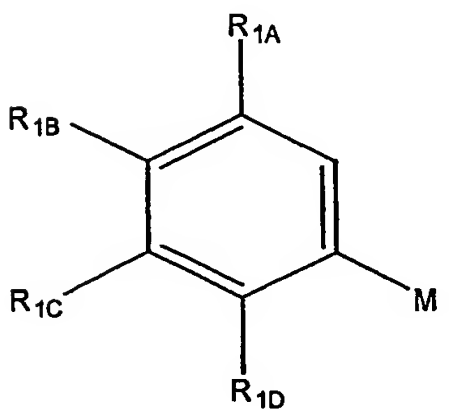
(b) reacting compound (6) with compound (7); or reacting compound 6(a) with compound 7(a);



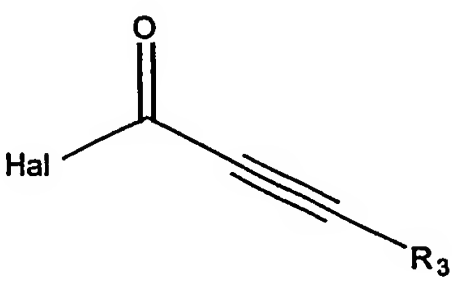
(6)



(7)

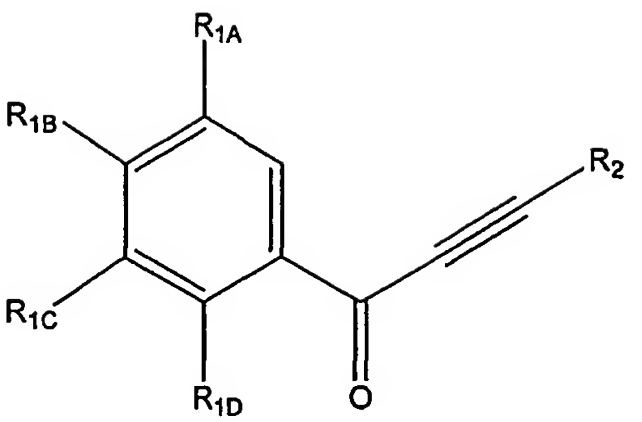


(6a)



(7a)

to form a compound (9)



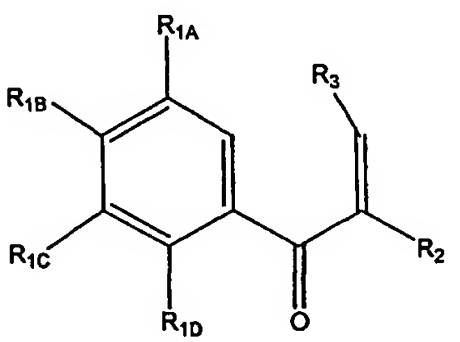
(9)

wherein

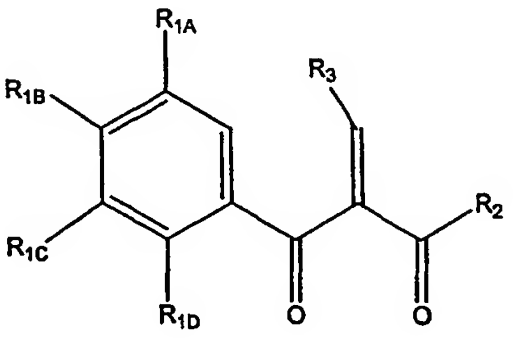
M is Li, Na, K or MgHal (Hal is Br, Cl or I);

b) treating compound (9) with a metal hydride in the presence of a palladium coupling agent;

c) coupling the resulting product with R_3-Hal or R_3-C(O)-Hal (wherein Hal is Cl, Br or I) to provide either compound (10) or (11); and



(10)

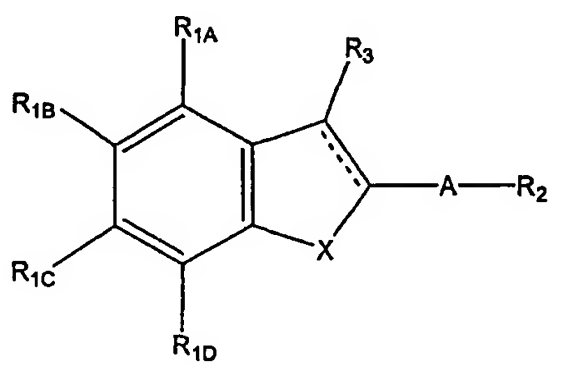


(11)

(d) cyclising (10) or (11) under acidic conditions to form an indanone and optionally treating the cyclised product with an oxidising agent to form an indenone.

18. A combinatorial library of compounds comprising at least two compounds of formula (I''') according to claim 17.

19. A method for preparing a compound of Formula (I'''')



(I'''')

wherein

X is O, S or NR (wherein R=H, C_{1-6}alkyl or $C(O)C_{1-6}$alkyl);

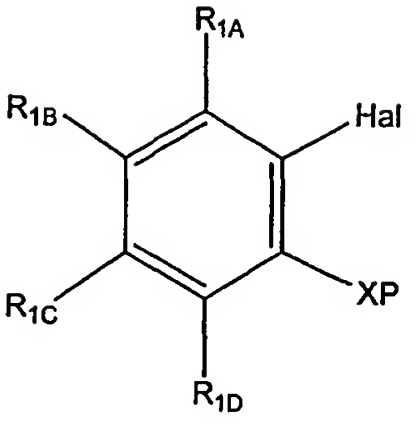
R_{1A}-R_{1D} are as defined in claim 1;

A is C=O, CH_2 or CH(OR') (wherein R' is H, C_{1-6}alkyl or C_{1-7}acyl); and

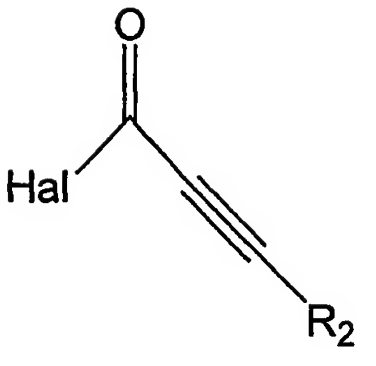
R_2 and R_3 are optionally substituted aryl groups;

comprising the steps of

a) coupling a compound (12) with compound (13)



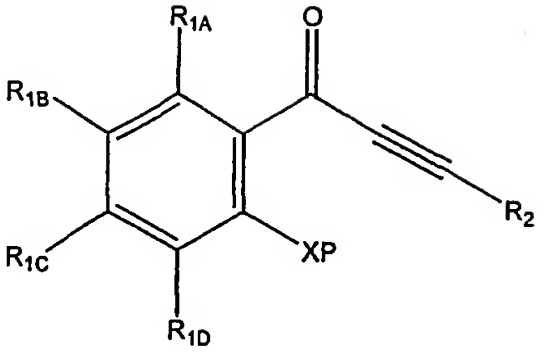
(12)



(13)

wherein Hal is Cl, Br, or I ,

to form a compound of formula (14);



(14)

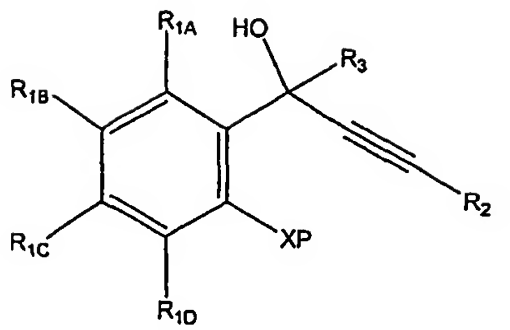
b) where X is S, protecting the thiol with a sulfur-protecting group

c) reacting (14) with a compound

M_1——R_3

wherein

M_1 is Li, Na, K, Mg, Cs or Ba, and R_3 is an optionally substituted aryl group; to form



(15)

wherein

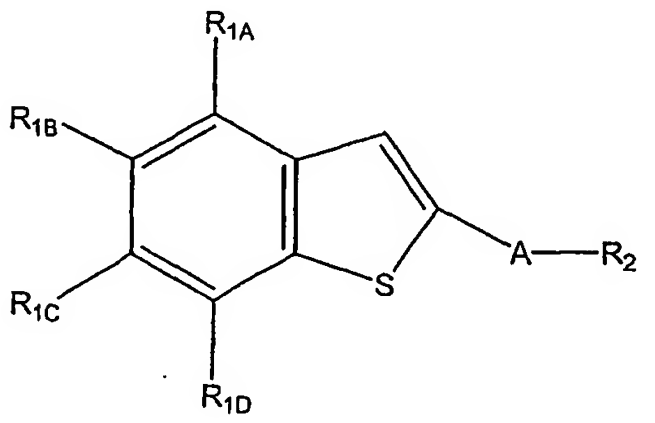
when X is O , then P is H and when X is S, P is a sulfur protecting group and when X is NR, R is a hydrogen, sulfonyl, C_{1-6}alkyl, C_{1-7}aryl, or an aryl group;

e) treating (15) with a Hal^+ producing reagent, to afford cyclisation;

e) and optionally reducing the cyclised product when A' is C=O, to afford libraries of compounds in which A' is CH_2 or CH(OR').

20. A combinatorial library of compounds comprising at least two compounds of formula (I"") according to claim 19.

21. A compound of Formula II



(II)

wherein

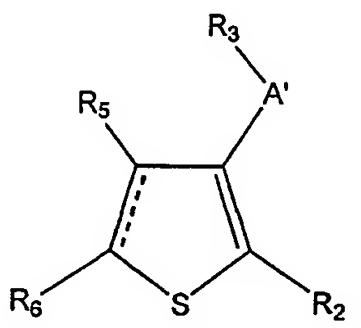
R_{1A}-R_{1D} are independently hydrogen, hydroxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted optionally substituted acyloxy, amino, optionally substituted alkylamino, optionally substituted dialkylamino or 2 adjacent R_{1A}-R_{1D} are O-CH_2-O;

R_2 and R_3 are optionally substituted aryl groups; and

A is C=O, CH_2 or CH(OR') (wherein R'=H, C_{1-6}alkyl or C_{1-7}acyl).

22. A combinatorial library of compounds comprising at least two compounds of formula II according to claim 21.

23. A compound of Formula (III)



(III)

wherein

R_2 and R3 are optionally substituted aryl groups;

A' is CO, CH_2, CH(OR') (wherein R'=H, C_{1-6}alkyl or C_{1-7}acyl) or a single bond;

R_5 and R_6 can independently be hydrogen, optionally substituted alkyl, optionally substituted aryl or optionally substituted alkenyl;

..... is an optional double bond.

24. A combinatorial library of compounds comprising at least two compounds of formula III according to claim 23.

25. A compound selected from the group consisting of:

6-methoxy-2-(4-methoxyphenyl)-3-3,4,5-trimethoxyphenyl)indole;

6-methoxy-2-(3-isopropoxy-4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)indole;

6-methoxy-2-(3-hydroxy-4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)indole;

6-methoxy-2-(3-isopropoxy-4-methoxyphenyl)-3-(3,4,5-trimethoxybenzoyl)indole;
6-methoxy-2-(3-hydroxy-4-methoxyphenyl)-3-(3,4,5-trimethoxybenzoyl)indole;
2,3-[2'-(3",4"-methylenedioxyphenyl)-3'-(3'",4'",5'"-trimethoxyphenyl)furano]-17-O-benzylestradiol;
6-methoxy-2-(4'-methoxyphenyl)-3-(3",4",5"-trimethoxybenzoyl)benzo[b]furan;
6-methoxy-2-(3-hydroxy-4-methoxyphenyl)-3-(3,4,5-trimethoxybenzoyl)benzo[b]furan;
6-methoxy-2-(4-methoxyphenyl)-3-[α-hydroxy-α-(3,4,5-trimethoxyphenyl)methyl]benzo[b]furan;
6-methoxy-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxybenzyl)benzo[b]furan;
6-methoxy-2-(3-hydroxy-4-methoxyphenyl)-3-[α-hydroxy-α-(3,4,5-trimethoxyphenyl)methyl}benzo[b]furan;
3-(3'-isopropoxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3",4",5"-trimethoxybenzoyl)-1-indanone;
3-(3'-isopropoxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3",4",5"-trimethoxybenzoyl)indenone;
3-(3'-hydroxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3",4",5"-trimethoxybenzoyl)indenone;
(±)trans-3-(3'-isopropoxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3",4",5"-trimethoxyphenyl)-1-indanone;
(±)trans-3-(3'-isopropoxy-4'-methoxyphenyl)-4,5,6-trimethoxy-2-(3",4",5"-trimethoxyphenyl)-1-indenone;
2-(3'-acetoxy-4'-methoxyphenyl)-4,5-dihydro-3-(3",4",5",-trimethoxyphenyl)thiophene;
2-(3'-acetoxy-3'-methoxyphenyl)-3-(3",4",5",-trimethoxybenzoyl)thiophene;
2-(3'-isopropoxy-4'-methoxyphenyl)-6-methoxy-3-(3",4"5"-trimethoxybenzoyl)benzo[b]thiophene;
2-(3'-hydroxy-4'-methoxyphenyl)-6-methoxy-3-(3",4",5"-trimethoxybenzoyl)benzo[b]thiophene;
2-(3'-hydroxy-4'-methoxyphenyl)-5,6-methylendioxy-3-(3",4"5"-trimethoxybenzoyl)benzo[b]thiophene;
3-(α-hydroxy-3'-hydroxy-4'-methoxybenzyl)-6-methoxy-3-(3",4"5"-trimethoxybenzoyl)benzo[b]thiophene;

5-isopropoxy-2-(3'-isopropoxy-4'-methoxybenzoyl)-6-methoxybenzo[b]thiophene;
5-hydroxy-2-(3'-hydroxy-4'-methoxybenzoyl)-6-methoxybenzo[b]thiophene;
5-isoporpoxy-2-(3'-isopropoxy-4'-methoxybenzoyl)-6-methoxy-3-(3",4",5"-trimethoxyphenyl)benzo[b]thiophene;
5-hydroxy-2-(3'-hydroxy-4'-methoxybenzoyl)-6-methoxy-3-(3",4",5"-trimethoxyphenyl)benzo[b]thiophene;
2-[α-(3"-isopropoxy-4"-methoxyphenyl)-3',4',5'-trimethoxybenzylidene]-5-isopropoxy-6-methoxybenzo[b]thiophen-3-one;
2-[2-oxo-1-(3'-isopropoxy-4'-methoxyphenyl)-2-(3",4"5"-trimethoxyphenyl)-ethylidene]-5-isopropoxy-6-methoxybenzo[b]thiophen-3-one.

26. Use of a compound according to claim 25 in the manufacture of a medicament to treat conditions which require an anti-mitotic agent.

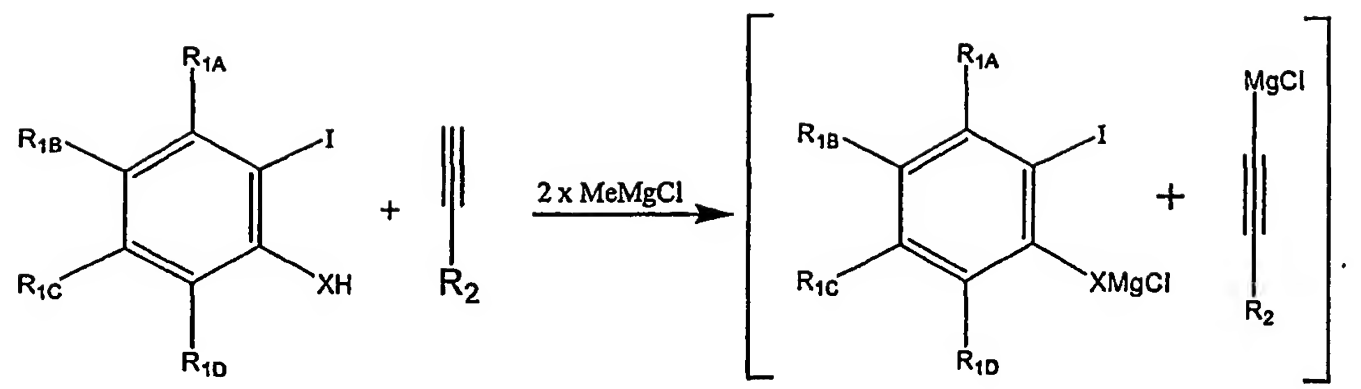
27. Use according to claim 26 wherein the condition to treat is a tumour.

28. A method of treating a condition requiring an anti-mitotic agent including administering to a subject in need thereof a compound according to claim 25.

29. A method according to claim 28 wherein the condition to be treated is a tumour.

30. A composition comprising a compound according to claim 25 together with a pharmaceutically acceptable carrier.

31. A kit of components to prepare a library of compounds to be used for screening for TPI activity said kit comprising at least two substrates selected from (a), (b) and (c) as defined in claim 1.



X = O, NR (R= acyl, sulfonyl, alkyl, or aryl)

Figure 1

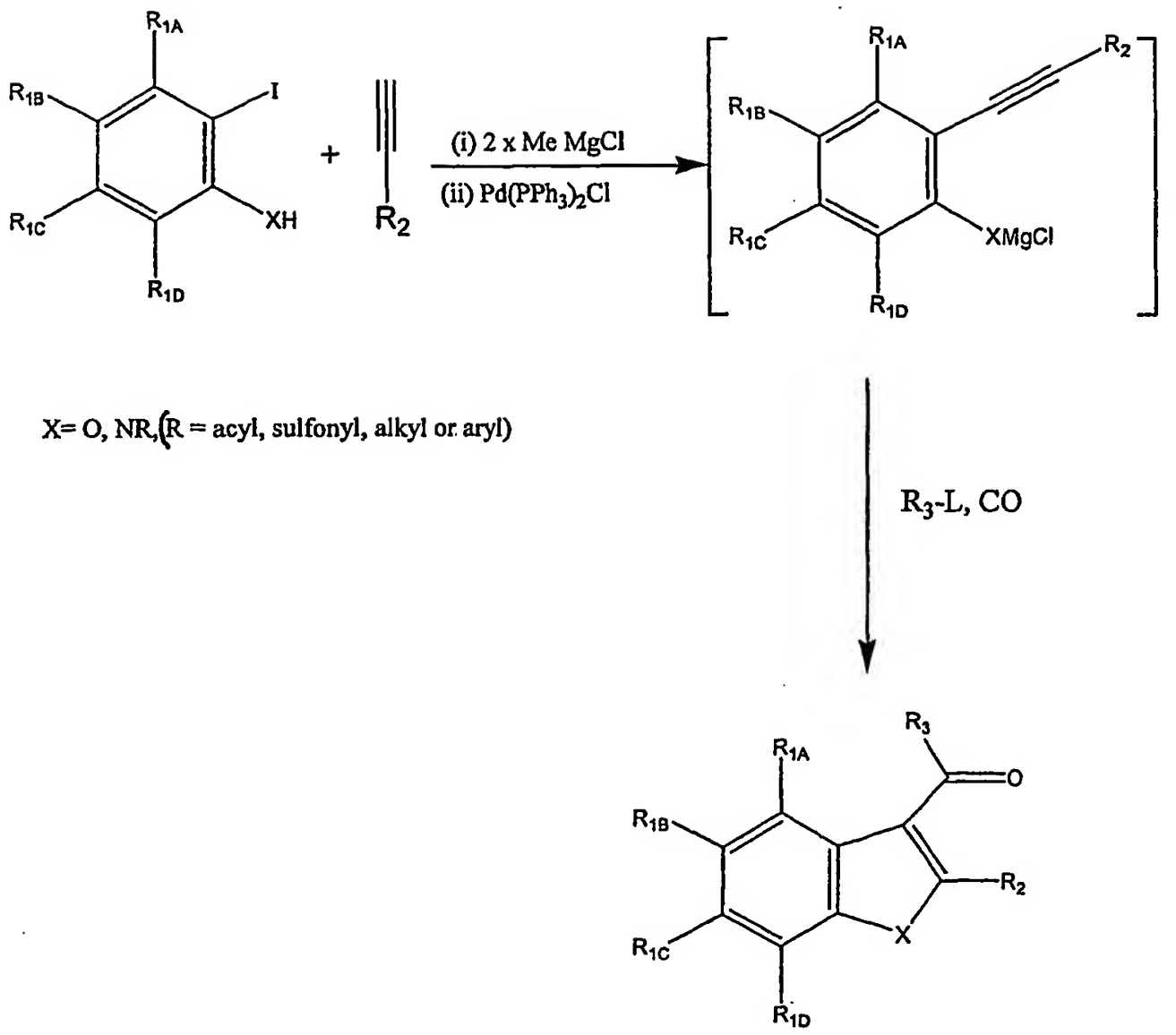

R1A
R1B
I
R1C
XH
R1D
+
R2
(i) 2 x Me MgCl
(ii) Pd(PPh3)2Cl
R1A
R2
R1B
R1C
XMgCl
R1D
X= O, NR, (R = acyl, sulfonyl, alkyl or aryl)
R3-L, CO
R3
O
R1A
R1B
R2
R1C
X
R1D

Figure 2

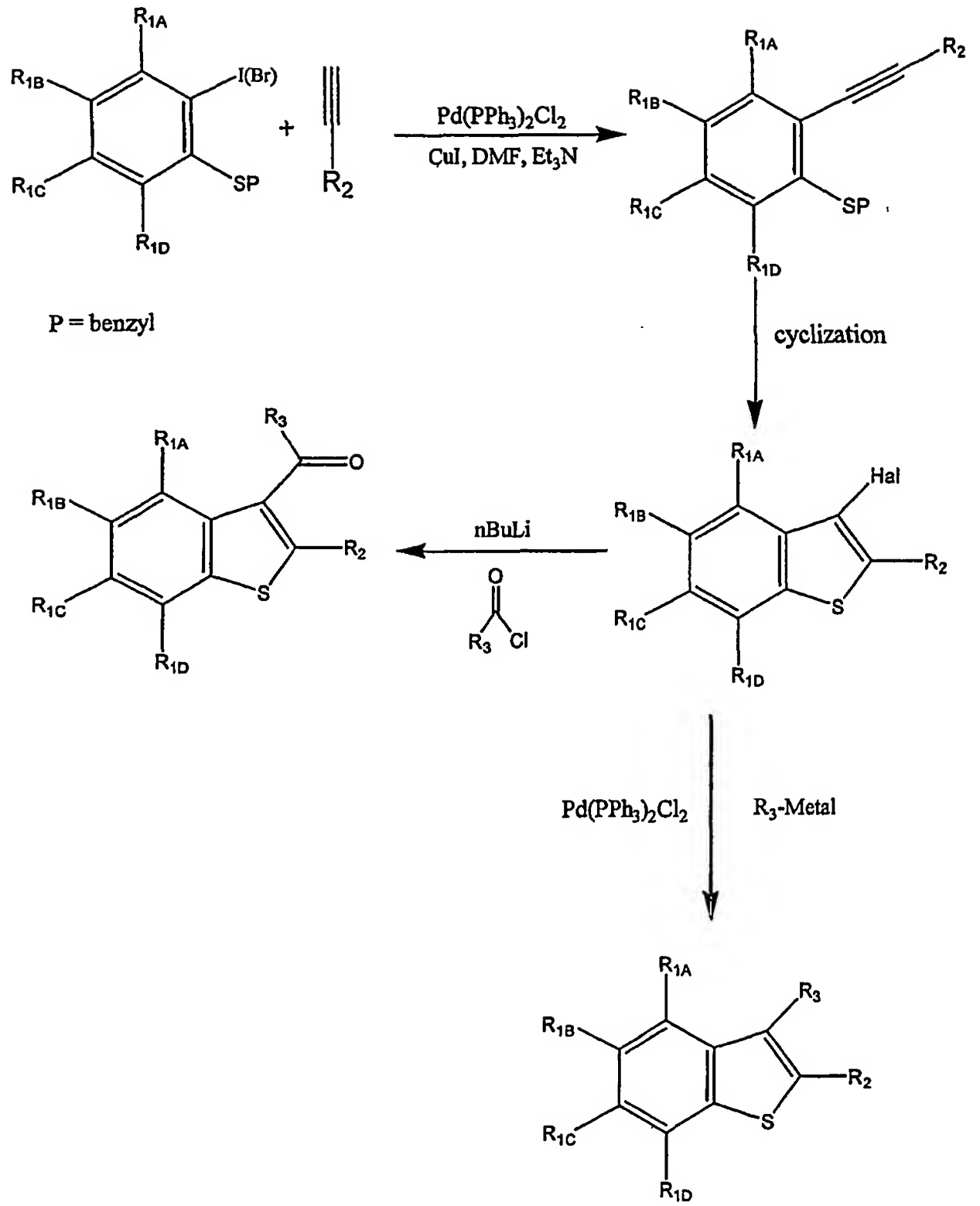
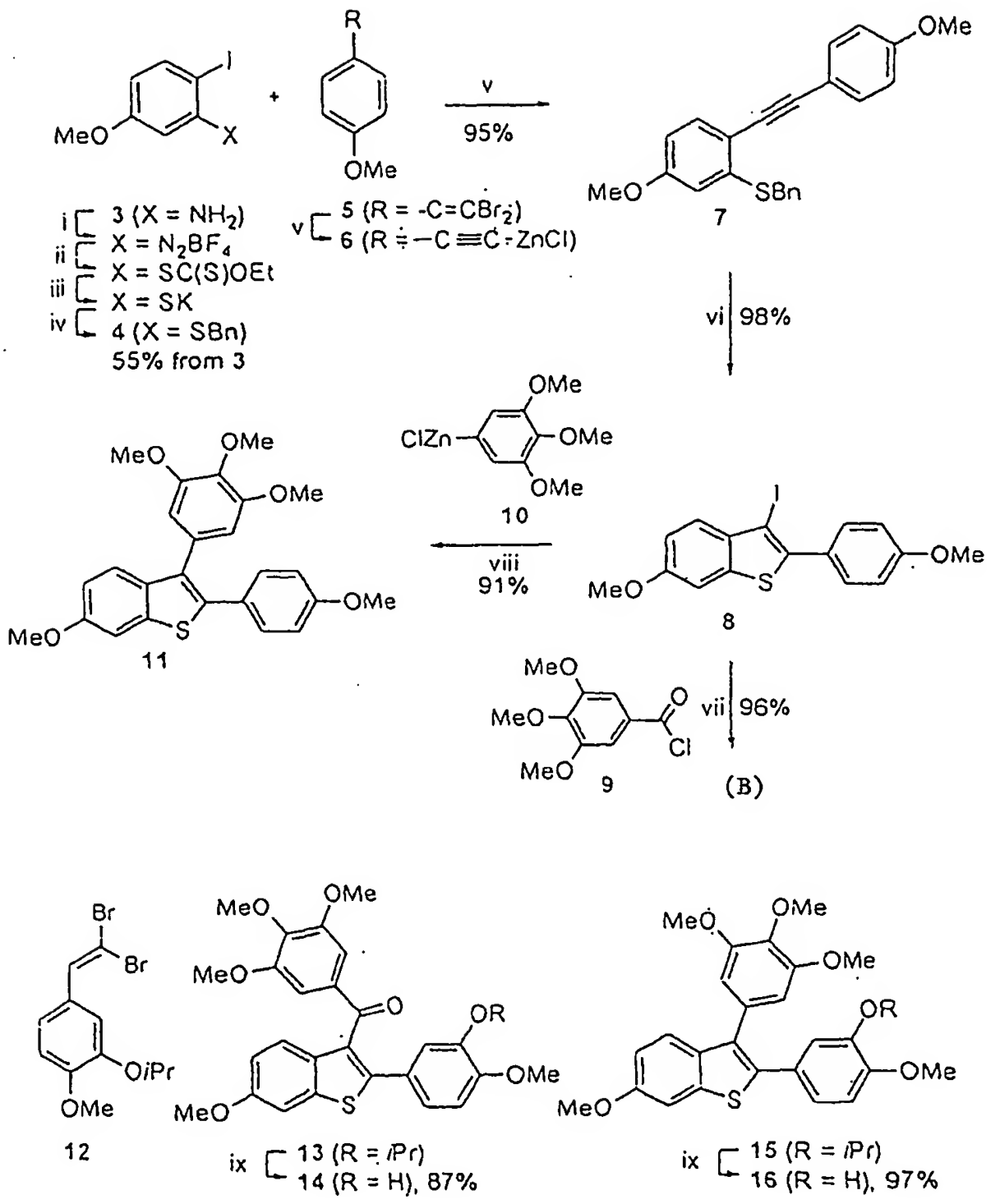
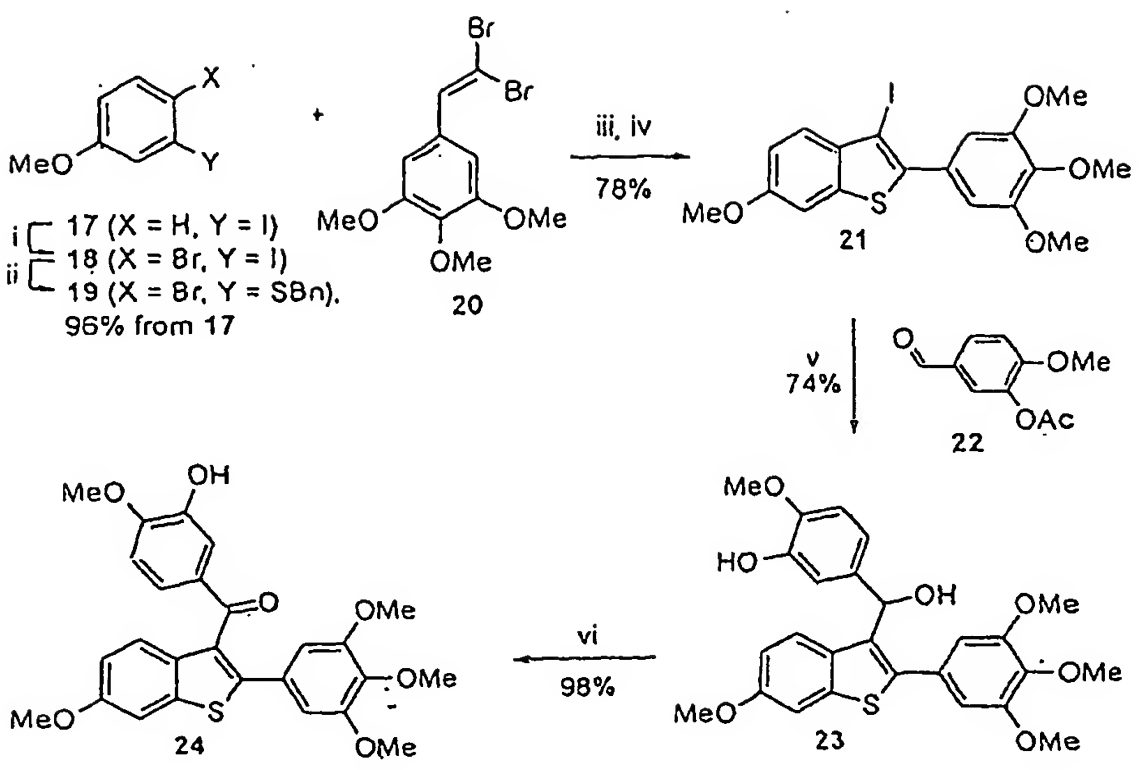

R1A
R1B
I(Br)
R1C
SP
R1D
+
R2
Pd(PPh3)2Cl2
CuI, DMF, Et3N
R1A
R2
R1B
R1C
SP
R1D
P = benzyl
cyclization
R1A
Hal
R1B
R2
R1C
S
R1D
nBuLi
O
R3 Cl
R3
O
R1A
R1B
R2
R1C
S
R1D
Pd(PPh3)2Cl2
R3-Metal
R1A
R3
R1B
R2
R1C
S
R1D

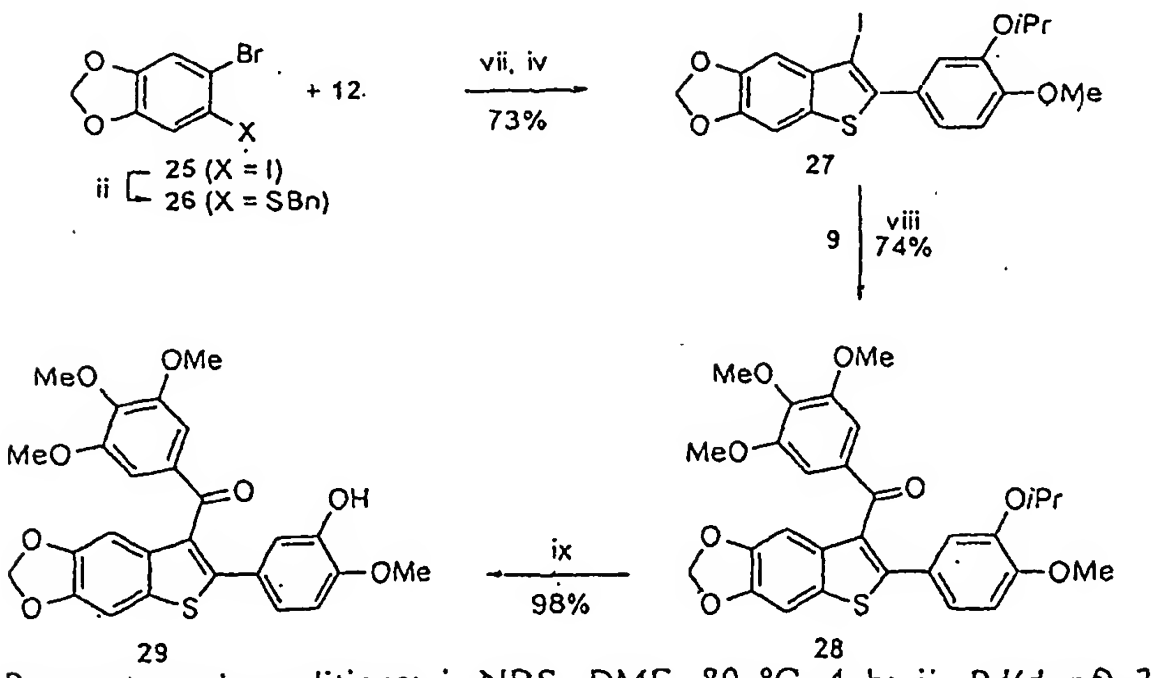
Figure 3



" Reagents and conditions: i. HBF_4, $NaNO_2$, H_2O: ii. KSC(C)OEt, DMF; iii. MeOH, KOH; iv. KOH(aq), BnCl, nBu_4NHSO_4 cat., CH_2Cl_2; v. 2 x nBuLi, THF, then $ZnCl_2$, $Pd(PPh_3)_2Cl_2$, 4; vi. I_2, CH_2Cl_2; vii. 2 x tBuLi, THF, 9; viii. 10 (from 3,4,5-trimethoxyiodobenzene, 2 x tBuLi, THF and $ZnCl_2$), $Pd(PPh_3)_2Cl_2$; ix. $AlCl_3$ 3 equiv., CH_2Cl_2.

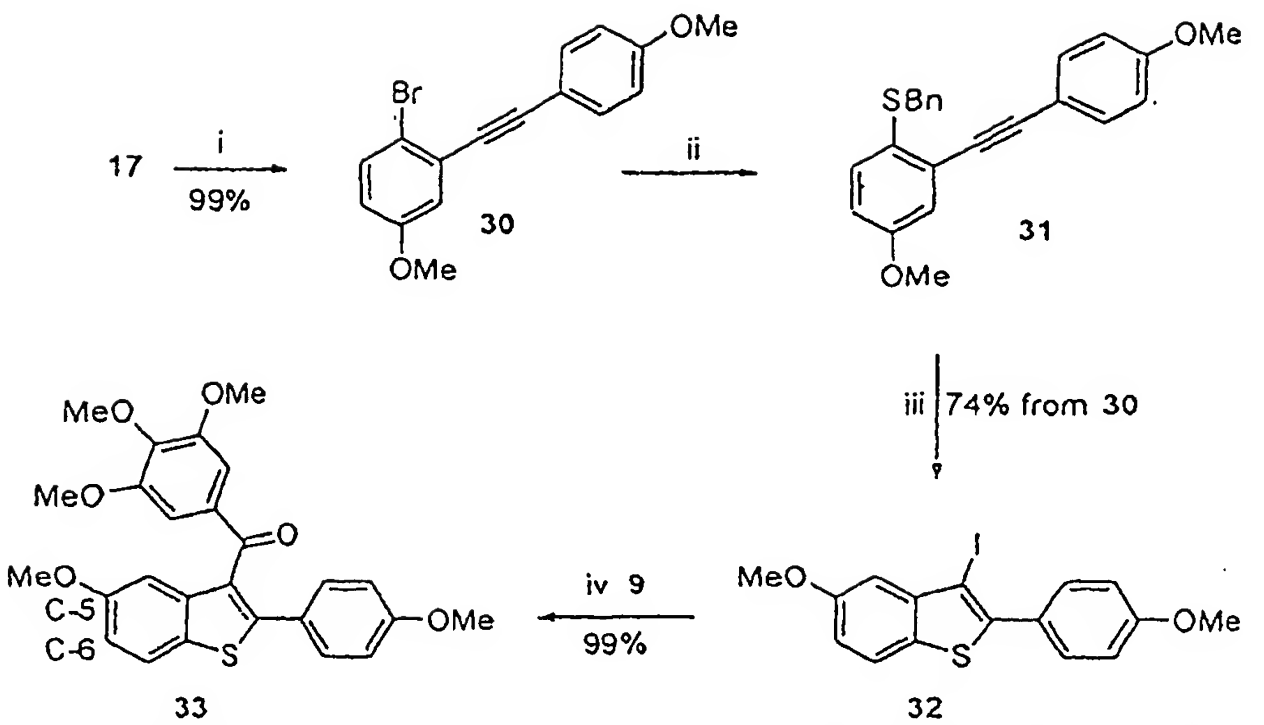
FIGURE 4





[a] Reagents and conditions: i. NBS, DMF, 80 °C, 4 h; ii. Pd(dppf) 3 mol%, BnSH, DMF, Et_3N, 70 °C, 3 h; iii. 20, 2 x *n*BuLi, THF, then $ZnCl_2$, $Pd(PPh_3)_2Cl_2$ 2 mol%, PPh_3 4 mol%, 17, DMF, 100 °C, 3 h; iv. I_2, CH_2Cl_2; v. *n*BuLi, THF, 22, then KOH in MeOH; vi. DDQ, CH_2Cl_2; vii. 12, 2 x *n*BuLi, THF, then $ZnCl_2$, $Pd(PPh_3)_2Cl_2$ 2 mol%, PPh_3 4 mol%, 26, DMF, 100 °C, 3 h; viii. *i*PrMgCl, THF, 9; ix. $AlCl_3$, 3 equiv., CH_2Cl_2.

FIGURE 5



[a] Reagents and conditions: i. 4-Methoxyethynylbenzene, $Pd(PPh_3)_2Cl_2$ 1.5 mol%, CuI 3 mol%, DMF, Et_3N; ii. *n*BuLi, THF, BnSSBn; iii. I_2, CH_2Cl_2; v. *n*BuLi, THF, 9.

FIGURE 6

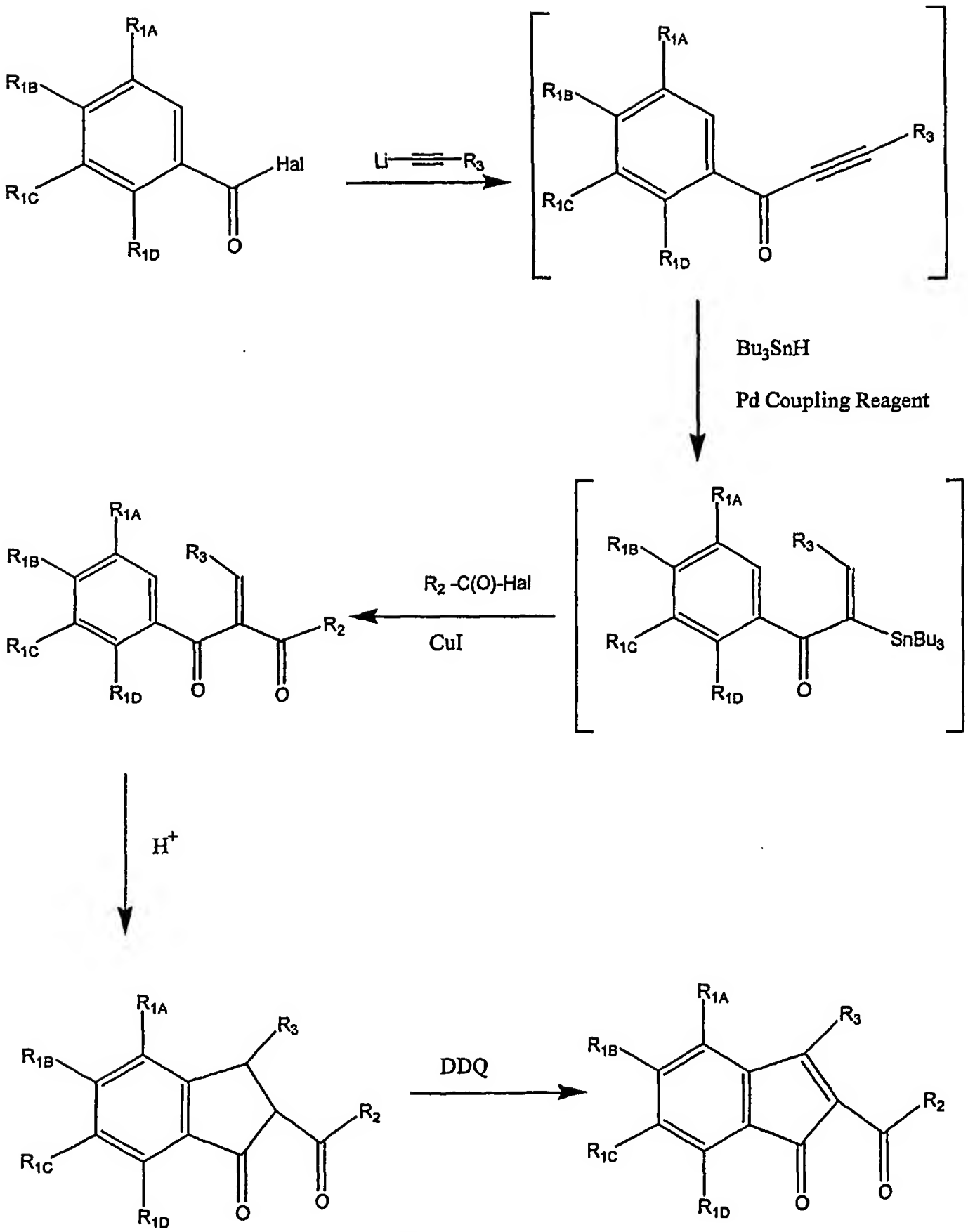

R1A
R1B
R1C
R1D
Hal
O
Li
R3
Bu3SnH
Pd Coupling Reagent
SnBu3
R2 -C(O)-Hal
CuI
H+
DDQ

FIGURE 7

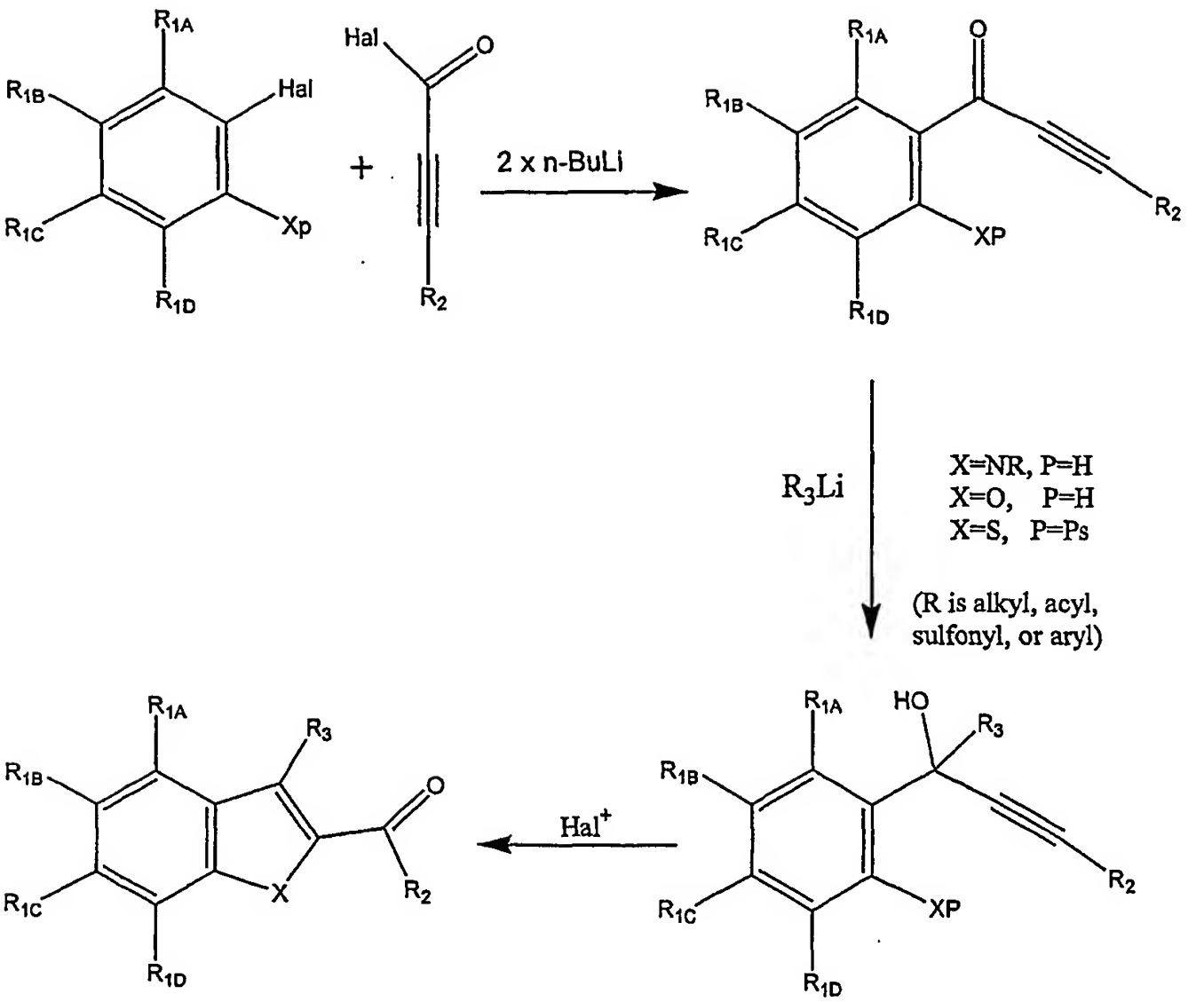

R1A
R1B
Hal
R1C
Xp
R1D
Hal
O
+
R2
2 x n-BuLi
R1A
O
R1B
R1C
XP
R1D
R2
R3Li
X=NR, P=H
X=O, P=H
X=S, P=Ps
(R is alkyl, acyl, sulfonyl, or aryl)
R1A
R3
R1B
O
R1C
X
R2
R1D
Hal+
R1A
HO
R3
R1B
R1C
XP
R1D
R2

FIGURE 8

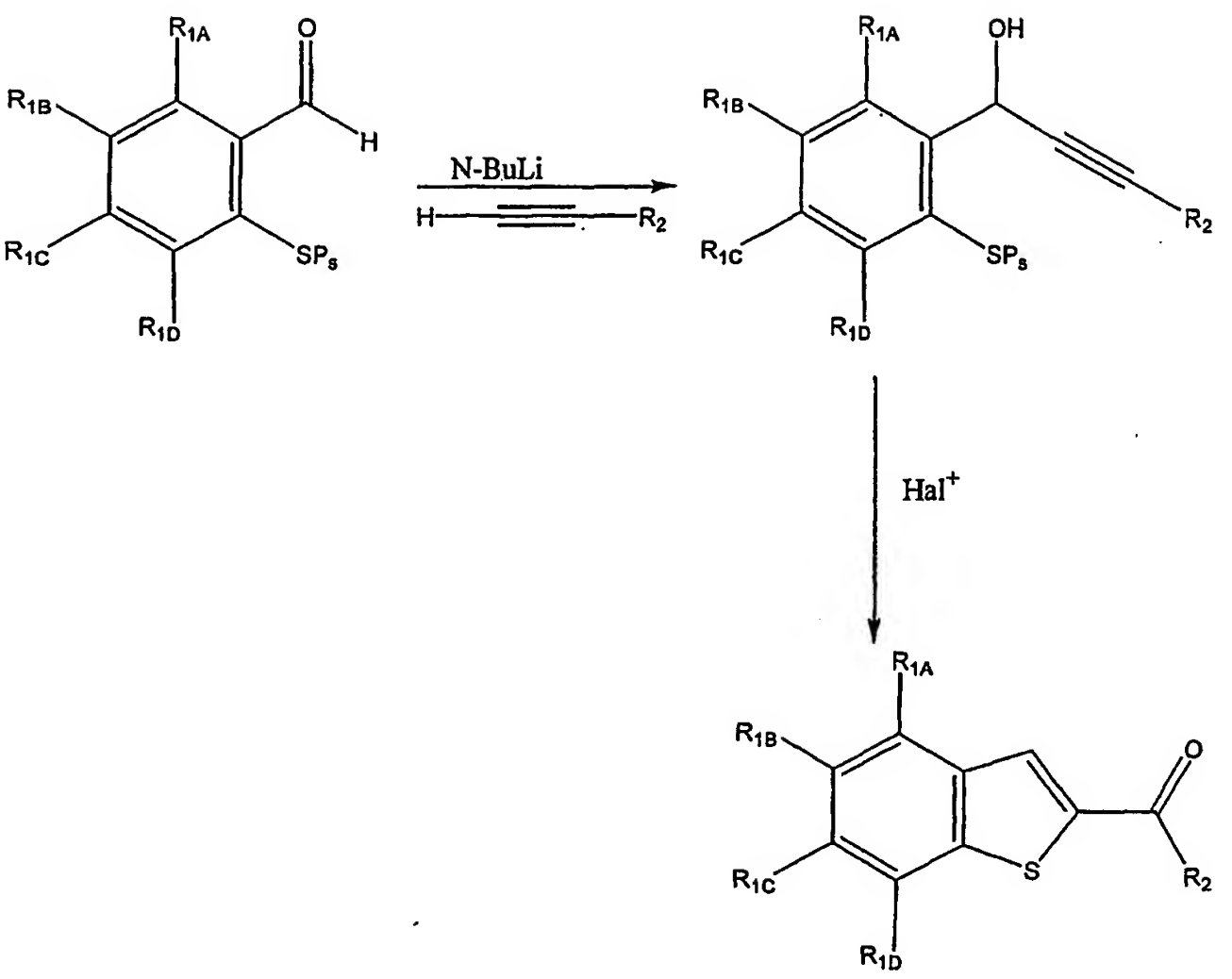


FIGURE 9

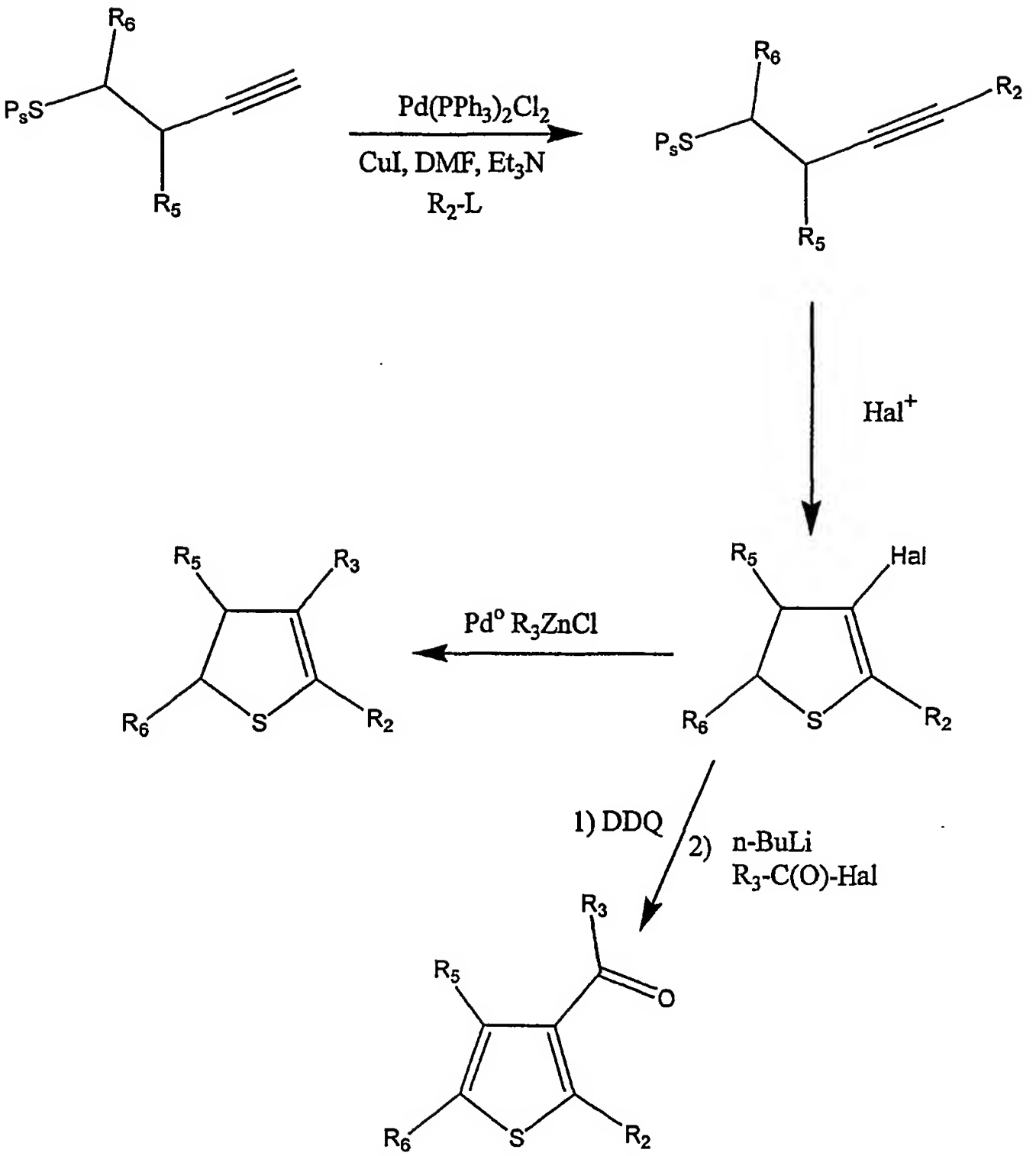
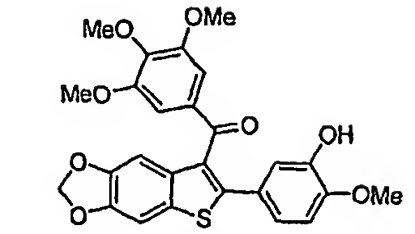
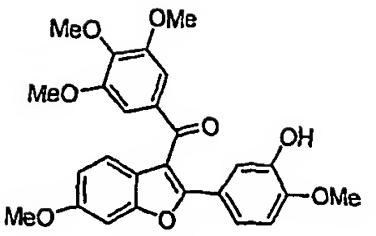

R6
PsS
R5
Pd(PPh3)2Cl2
CuI, DMF, Et3N
R2-L
R6
R2
PsS
R5
Hal+
R5
Hal
R6
S
R2
Pd° R3ZnCl
R5
R3
R6
S
R2
1) DDQ
2) n-BuLi
R3-C(O)-Hal
R3
O
R5
R6
S
R2

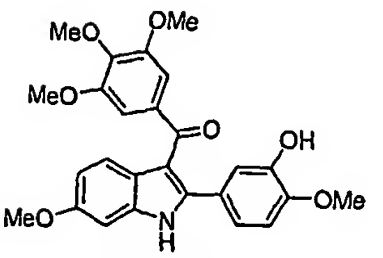
FIGURE 10



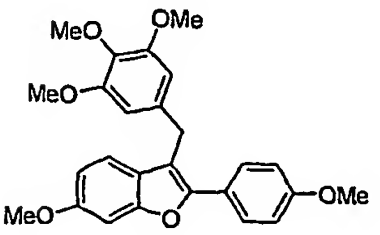
BLF-53-3



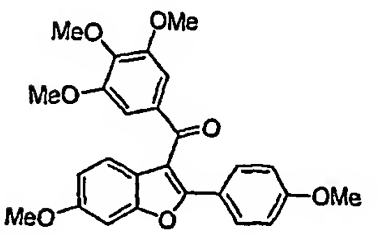
BLF-62-3



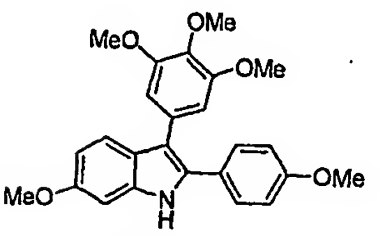
BLF-67-3



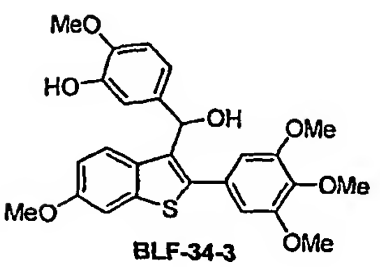
BLF-70-3



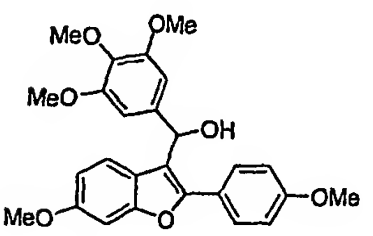
BLF-28-1



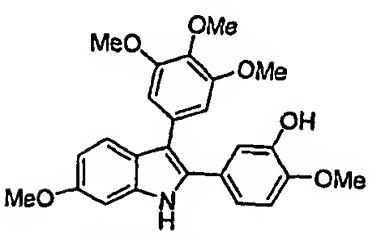
BLF-36-1



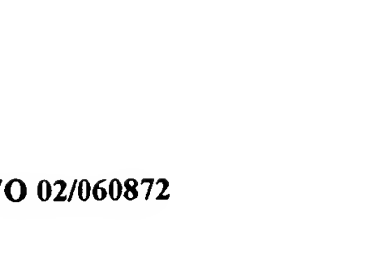
BLF-34-3



BLF-68-3



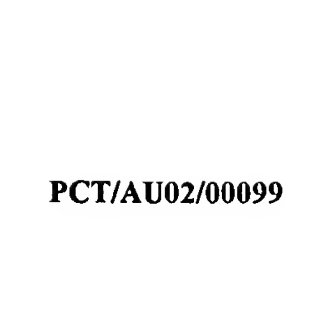
BLF-61-3



BLF-69-3

BLF-86-1

GPF-60-1



BLF-89-3

KH-2-2

DK-12a-1

racemic DK-2a-2

FIGURE 11

INTERNATIONAL SEARCH REPORT	International application No. PCT/AU02/00099

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07D 209/02, 307/80, 307/86, 333/16, 333/22 333/26, 333/62, 495/04; C07C 45/72, 49/255, 49/755, 323/20, 323/22; C07J 71/00; A61K 31/404, 31/343, 31/381, 31/122; A61P 35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN File CA substructure search and keywords including tubulin and tumour
Molecular Formula Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 98/39323 A1 (BAYLOR UNIVERSITY) 11 September 1998 See claim 1, 11, 18, 31 and 33	7-11, 25-31; 2(F), 2(G), 6
X	EP 897918 A1 (ELI LILLY AND COMPANY) 24 February 1999 See page 3 formula I(a), I(b); page 7 compounds 2, 4, 7-8, 13-17, 23-29, examples 1-11	7, 21
Y		2(G), 6
X	FR 2752576 A1 (ADIR) 27 February 1998 See formulas (III) and (X) and the table on page 17	23

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2002	30 APR 2002
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **CHRISTINE BREMERS** Telephone No : (02) 6283 2313

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU02/00099

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	US 5705525 (WIERZBICKI et al) 6 January 1998	
X	See formula (II), example 1, columns 1, 3-4 (central compound), 14-18, 20	23
	EP 838461 A2 (ELI LILLY AND COMPANY) 29 April 1998	
X	See Scheme I compound VII	7, 11
Y		2(E), 6
	WO 95/00501 A2 (MERCK FROSST CANADA INC.) 5 January 1995	
X	See Table I examples 1-3, 13-14, Table II pages 68-70	23
A		12
	JP 5222073 (SUMITOMO PHARMACEUT CO LTD) 31 August 1993	
X	See page 18 compound 0051	7, 11,
Y		2(E), 6
	WO 91/19708 A1 (FUJISAWA PHARMACEUTICAL CO., LTD) 26 December 1991	
X	See claims 1-4	23
	JP 3043744 (HITACHI CHEM CO LTD) 25 February 1991	
X	See page 451 column 2 last two compounds, page 452 column 1 first three compounds	7, 8, 11
Y		2(E), 6
	JP 2024664 (CANON INC) 26 January 1990	
X	See compounds (1), (2), (5)-(7), (9)-(12), (14)-(20), (23)-(28), (30), (32), (33), (36),	7, 8
Y	(38)-(42), (46), (48) and last two compounds on page 592	2(E), 6
	US 4749712 (HABER) 7 June 1988	
X	See formulas I and II, examples 1-18, Table I, claims 1-14	23
	US 4495196 (BOSWELL) 22 January 1985	
X	See column 1 first compound, column 2 formula I, Tables IV and VI, claim 1	7, 8
Y		2(E), 6
A		12
	US 4432974 (HABER) 21 February 1984	
X	See column 4 formula II, examples 1, 2, 21	23
	EP 87629 (E. I. DU PONT DE NEMOURS AND COMPANY) 7 September 1983	
X	See claim 18	23
	EP 55470 (E. I. DU PONT DE NEMOURS AND COMPANY) 7 July 1982	
X	See formulas I and II on page 5, claims 1-11	23
A		12
	EP 55471 (E. I. DU PONT DE NEMOURS AND COMPANY) 7 July 1982	
X	See formulas I on page 2 and II on page 5	23
A		12
	US 4269828 (FLORA, L et al) 26 May 1981	
X	See column 4	7, 8
Y		2(E), 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU02/00099

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	US 4174405 (RELYEA, D. I. et al) 13 November 1979	
X	See columns 1-5 and 11, examples 9 and 11 compounds 24-41 claims	23
	US 4075227 (JONES, C. D. et al) 21 February 1978	
X	See columns 1and and formula (VI) in column 4	7
Y		2(E), 2(G), 6
	US 3565912 (SZMUSZKOVICZ) 23 February 1971	
Y	See formulas II, III, IV and V	2(E), 6
	US 3420838 (SZMUSZKOVICZ) 7 January 1969	
X	See formulas II and III, examples 1-4, 7, 9-19, 23-25, 27-29, 32-70	7, 8, 11
Y		2(E), 6
	GB 1108830 (THE UPJOHN COMPANY) 3 April 1968	
X	See page 1 formula I, claim 1	12
	BANWELL, M. G. Synthesis, X-Ray Crystal Structure and Tubulin-Binding Properties of a Benzofuran Analogue of the Potent Cytotoxic Agent Combretastatin A4. Australian Journal of Chemistry. 1999, vol 52 no 8 pages 767-774	
X	See pages 767 and 768 compounds (2), (4), (8), (14)-(16); page 770 "Conclusion", page 773 column 1	1, 2(E), 3-11, 13-20, 31
Y		14, 16
Y1		1-31
	MEDARDE, M et al, Synthesis and Pharmacological Activity of Diarylindole Derivatives. Cytotoxic Agents Based On Combretastatins. Bioorganic & Medicinal Chemistry Letters 1999, vol 9 pages 2303-2308	
X	See page 230 compounds 4a-4e	7, 8, 11
Y		2(E), 6
	DONNELLY, D. M. X et al, Aryllead Mediated Synthesis of Isoflavanone and Isoflavone Derivatives. Tetrahedron 1993, vol 49 no 36 pages 7967-7976	
X	See Table 1 and the last two compounds of Table 4	7, 8
Y		2(E), 6
	VICENTE, J et al, Palladium-assisted Formation of Carbon-carbon Bonds. Stoichiometric Synthesis of Indenols and Indenones. Catalytic Synthesis of an Indenol. Journal of Organometallic Chemistry. 1992, vol 436 pages C9-C12	
X	See page C10 compound 2	7, 8
Y		2(L), 6
	STROHMEIER, J et al. Synthesis and Estrogen Receptor Affinity of 2,3-Diaryindoles. Arch. Pharm.(Weinheim). 1987,vol 320,pages 407-417	
X	See page 407, page 408 compounds 3a-7a, 10a, 11a, 13a, page 409 compound 15, 17a	7
Y		2(E), 6
	Chemical Abstracts, 1970, vol 72 abstract no 66818, YAMAMOTO, H. et al	
X	See whole abstract	7, 8, 11
Y		2(E), 6
X	CAS Registry Number 41046-70-2	31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU02/00099

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAS Registry Number 768-60-5	31
Y2	Molecular Diversity and Combinatorial Chemistry. Libraries and Drug Discovery. ACS Symposium Series. Published by the American Chemical Society, Washington, D.C. Edited by I. M. Chaiken and K. D Janda. 1996 ISBN 0-8412-3450-7 See Preface	1-31
Y3	Combinatorial Chemistry. Synthesis, Analysis, Screening. Published by Wiley-VCH Wienheim. Edited by G. Jung. 1999. See Preface	1-31
P,X P,Y	WO 01/68654 A2 (BAYLOR UNIVERSITY) 20 September 2001 See claims 1-24, 41-44, 60, 65, Fig 2, Fig 8c second product, Fig 10 first compound, Fig 13 compound 36	7-9, 11, 25-31 2(E), 6
P,X P,Y	WO 01/19794 A2 (BAYLOR UNIVERSITY) 22 March 2001 See claims 1-12, 14,-17, 28-36, Fig 9, Fig 10	7, 25-31 2(F), 2(G), 6

Any Y document may be combined with any of Y1, Y2 or Y3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU02/00099

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :

because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos : **1-31 (all in part)**

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

A full search was not possible on economic and technical grounds because of the breadth of the claims. Even a conservative substructure search yielded too many answers and so had to be limited by keywords. This is therefore by no means a complete search.

3. ☐ Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU02/00099

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	9839323	AU	66886/98	EP	984954	US	5886025
		US	6162930	US	2001034454		
EP	897918	AU	86952/98	US	5908859	WO	9907694
FR	2752576	NONE					
US	5705525	AU	45675/96	CA	2170097	CN	1142496
		EP	728755	FI	960795	FR	2730996
		JP	8253470	NO	960706	NZ	286045
		ZA	9601472				
EP	838461	CA	2214872	JP	10130260	US	5843940
		US	6121293				
WO	9500501	AU	69674/94	AU	61970/96	AU	19132/97
		BG	100247	BR	9406979	CA	2176973
		CA	2176974	CA	2163888	CN	1125944
		CN	1295065	CZ	9503146	EP	705254
		EP	754687	EP	822190	EP	980866
		FI	956119	FI	20012510	HR	940373
		HU	74070	IL	110031	JP	2000038375
		LV	12209	MX	9404749	NO	955256
		NZ	267386	PL	312196	SG	52703
		SK	1502/95	ZA	9404501	US	5474995
		US	5536752	US	5550142	US	5710140
		US	5840746	US	6239173	US	2001016595
		AU	12694/95	BG	100350	BR	9408478
		CA	2180651	CN	1143365	EP	739340
		FI	962800	HU	74986	NO	960393
		SG	43841	WO	9518799	AU	72736/96
		EP	904269	US	6057319	WO	9716435
		US	5698584	AU	56215/94	CA	2151235
		EP	673366	US	5604260	WO	9413635

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU02/00099

Patent Document Cited in Search Report		Patent Family Member					
		GB	2283745	US	5436265	AU	36139/95
		EP	785778	IL	115505	WO	9611676
		ZA	9508558	CA	2202345	EP	863134
		JP	10251220	PL	319742	AU	61788/94
		CA	2157107	US	5409944	WO	9420480
WO	9119708	AU	79731/91	CN	1059142	EP	593761
		IE	911942	PT	97906	US	5571810
		ZA	9104241				
US	4749712	NONE					
US	4495196	AU	61711/80	DK	3502/80	EP	25884
		ES	494546	ES	8106498	FI	802693
		GR	69839	JP	56049355	NO	802528
		PT	71748	ZA	8005280		
US	4432974	NONE					
EP	87629	AU	11460/83	CA	1242725	DK	676/83
		ES	520218	ES	8403884	FI	830523
		GR	78135	IL	67940	JP	58159489
		NO	830527	NZ	203317	PH	18061
		PT	76247	SU	1250172	ZA	8301046
		US	4590205	US	4820827		
EP	55470	DK	5792/81	JP	57134480	US	4381311
EP	55471	DK	5791/81	JP	57134479	US	4427693
US	4269828	AU	34511/78	CA	1109794	DE	2813165
		FR	2385398	GB	1588284	IT	1095497
		JP	54002340	NL	7803247	NZ	186810
		PH	17483	PH	17488	PH	18798
		PH	18911	ZA	7801751	PH	17484
		US	4264582	US	4216212	US	4282214
		BE	865370	US	4275059	CH	645542
		SE	7806449				
US	4174405	AU	77451/75	CA	1072967	CA	1072880
		FR	2261704	JP	50117922	ZA	7500270

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU02/00099

Patent Document Cited in Search Report		Patent Family Member					
		CA	1086643	DE	2724494	FR	2353228
		GR	63207	IL	52173	JP	52148067
		NL	7706027	IL	47687		
US	4075227	AR	216451	AT	8007/76	AU	17408/76
		BE	847718	BG	27554	CA	1064031
		CH	626360	DE	2647864	DK	4845/76
		ES	452737	FR	2329270	GB	1572506
		GR	62400	IL	50413	JP	52053852
		NL	7611972	NZ	182428	PT	65753
		SE	7611954	ZA	7606442		
US	3565912	NONE					
US	3420838	CH	487148	DE	1620652	GB	1160064
		GB	1160065	IL	26912	NL	6617598
JP	5222073	NONE					
JP	3043744	NONE					
JP	2024664	NONE					
GB	1108830	NONE					
WO	0168654	NONE					
WO	0119794	NONE					

END OF ANNEX